

## REVIEW ARTICLE

## Bidirectional regulatory mechanisms of lipids and radiotherapy: Metabolic disorders, therapeutic interventions, and pan-cancer clinical insights

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## Abstract

Malignant tumors continue to pose a significant threat to global health. Emerging evidence suggests that abnormal blood lipid levels may influence tumor incidence, and cancer patients frequently exhibit dysregulated lipid profiles. Radiotherapy, a cornerstone in cancer treatment, has been demonstrated to modulate blood lipid levels in patients. Conversely, blood lipid concentrations can significantly impact the efficacy of radiotherapy and the incidence of associated complications. This comprehensive review delves into cutting-edge research illuminating the intricate bidirectional interplay between blood lipid profiles and radiotherapy efficacy in malignant tumor patients. At the same time, it investigates the promising potential of tailored dietary modulation strategies and novel lipid-lowering therapeutics to enhance treatment efficacy and patient prognosis.

**Keywords:** Radiotherapy; Blood lipids; Cancer; Lipid metabolism; Therapeutic efficacy

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## 1. Introduction

Malignant tumors remain the leading cause of mortality worldwide.<sup>1</sup> According to the Global Cancer Statistics 2022 report, there were approximately 19.97 million new cancer cases and 9.74 million cancer-related deaths globally in 2022.<sup>2</sup>

Blood lipids, encompassing triglycerides (TG), cholesterol, cholesterol esters, phospholipids, and free fatty acids, play a crucial role in cellular metabolism. Emerging evidence suggests that tumorigenesis in specific cancer types may be accompanied by dysregulated blood lipid metabolism. For instance, a lipid analysis of serum samples from 100 breast cancer patients and 100 healthy controls revealed elevated levels of low-density lipoprotein (LDL), TG, and total cholesterol (TC) in cancer patients compared to healthy individuals, underscoring the prevalence of dyslipidemia in cancer populations.<sup>3</sup>

Radiotherapy, a primary modality in cancer treatment, exerts its therapeutic effects through the induction of DNA damage in malignant cells.<sup>4</sup> A growing body of evidence indicates that radiotherapy can significantly alter patients' blood lipid profiles.

Conversely, blood lipid levels can influence radiotherapy's efficacy and safety profile.

This review aims to provide a comprehensive analysis of current clinical studies, focusing on the effects of radiotherapy on blood lipid levels and the impact of blood lipids on radiotherapy outcomes. The ultimate goal is to offer evidence-based insights for optimizing lipid management in radiotherapy patients.

## 2. The impact of radiotherapy on blood lipids in cancer patients

A systematic literature search was conducted across PubMed, EMBASE, Cochrane Library, and Web of Science, yielding 10 relevant studies (Table 1). Despite methodological and population differences, all studies consistently demonstrated that radiotherapy significantly alters blood lipid profiles in cancer patients.

### 2.1. Head-and-neck tumors

Squamous cell carcinoma is the predominant histological type of head-and-neck cancer, accounting for over 90% of all cases. In 2022, there were approximately 660,740 newly diagnosed cases worldwide.<sup>5</sup> Smoking, heavy alcohol consumption, and human papillomavirus infection are the most significant risk factors for head-and-neck cancer.<sup>6</sup> Jelonek *et al.*<sup>7</sup> conducted a study on head-and-neck squamous cell carcinoma patients, dividing them into three treatment groups: radiotherapy alone ( $n = 18$ ), concurrent chemoradiotherapy with cisplatin ( $n = 16$ ), and chemotherapy alone ( $n = 13$ ).<sup>7</sup> Mass spectrometry analysis of pre- and post-treatment serum samples revealed significant decreases in phosphatidylcholine (PC) levels in both radiotherapy groups, with more pronounced reductions in the concurrent chemoradiotherapy group. Subsequent analysis demonstrated a negative correlation between serum PC levels and radiation dose/absorbed

**Table 1. Radiotherapy effects on blood lipid levels in cancer patients**

Author (s)	Year	Diagnosis	Tumor staging	Sample size	Method	Types of lipids	Effect	Baseline
Jelonek <i>et al.</i> <sup>7</sup>	2020	HNSCC	TxNxM0	47	LC-MS	PCs	Low	-
Jelonek <i>et al.</i> <sup>8</sup>	2021	HNSCC	TxNxM0	45	LC-MS	PCs	Low	-
Tang <i>et al.</i> <sup>10</sup>	2020	Lung cancer	NA	256	LC-MS	S1P	Low	Receiving radiotherapy compared to non-radiotherapy patients (222.13±48.63 vs. 315.16±51.06)
Lv <i>et al.</i> <sup>11</sup>	2024	NSCLC	Histology grade III-IV	31	LC-MS	PS, PI, and TC	Low	-
Zemanova <i>et al.</i> <sup>13</sup>	2016	ESCC	Histology grade II-III	42	LC-MS	PC	High	Healthy compared to patients (5.53±1.23 vs. 5.17±1.11)
Xu <i>et al.</i> <sup>15</sup>	2024	Cervical cancer	Histology grade I-IV	114	LC-MS	FFA	Most high	-
Ng <i>et al.</i> <sup>17</sup>	2020	HCC	NA	47	LC-MS	FFA and GPL	High	-
Wolny-Rokicka <i>et al.</i> <sup>18</sup>	2019	Prostate cancer	NA	91	Roche/Hitachi Cobas C Systems	HDL	Low	-
Shaikh <i>et al.</i> <sup>19</sup>	2017	Breast cancer	NA	130	Gas chromatography	TC and LDL-C	Low	-
Giskeødegård <i>et al.</i> <sup>20</sup>	2022	Breast cancer	I-III	250	NMR spectroscopy	HDL, LDL-C, and TG	HDL low, LDL-C high, and TG high	-

Note: NA refers to not available.

Abbreviations: ESCC: Esophageal squamous cell carcinoma; FFA: Free fatty acids; GPL: Glycerophospholipids; HCC: Hepatocellular carcinoma; HDL: High-density lipoprotein; HNSCC: Head-and-neck squamous cell carcinoma; LC-MS: Liquid chromatography-mass spectrometry; LDL-C: Low-density lipoprotein cholesterol; NMR spectroscopy: Nuclear magnetic resonance spectroscopy; NSCLC: Non-small cell lung cancer; PC: Phosphatidylcholine; PI: Phosphatidylinositol; PS: Phosphatidylserine; S1P: Sphingosine-1-phosphate; TC: Total cholesterol; TG: Triglycerides.

energy, highlighting the significant impact of radiotherapy on lipid metabolism in head-and-neck squamous cell carcinoma patients.<sup>8</sup>

## 2.2. Thoracic tumors

Lung cancer is the most commonly diagnosed cancer, with approximately 1.8 million new cases each year. It is also the leading cause of cancer-related deaths, accounting for approximately 1.59 million deaths annually.<sup>9</sup> Sphingosine-1-phosphate (S1P), a bioactive lipid, has been implicated in lung cancer progression and treatment resistance. Tang *et al.*<sup>10</sup> analyzed serum S1P levels in 256 lung cancer patients, revealing significantly lower levels in the 124 patients receiving radiotherapy than in non-radiotherapy patients (222.13 s 48.63 vs. 315.16 ± 51.06). This inverse correlation (Spearman's rho = -0.653,  $p < 0.001$ ) suggests radiotherapy-induced modulation of S1P signaling.<sup>10</sup> Lv *et al.*<sup>11</sup> conducted a prospective study using mass spectrometry to analyze plasma lipid profiles in 31 advanced non-small cell lung cancer patients before and after radiotherapy. Significant reductions in phosphatidylserine, TC, and phosphatidylinositol (PI) levels were observed post-radiotherapy, indicating substantial alterations in lipid metabolism.<sup>11</sup>

In the 2022 global cancer statistics, esophageal cancer ranked seventh in incidence among all cancer types and sixth in mortality.<sup>12</sup> Zemanova *et al.*<sup>13</sup> investigated plasma PC fatty acid composition in 42 patients before and after neoadjuvant chemoradiotherapy in esophageal squamous cell carcinoma. The study revealed increased levels of docosahexaenoic acid and total n-3 polyunsaturated fatty acids post-treatment, suggesting radiotherapy-induced modifications in fatty acid metabolism.<sup>13</sup>

## 2.3. Abdominal tumors

Cervical cancer ranks fourth in incidence among malignancies in women, with China and India accounting for more than one-third of global cases. Among women aged 20 – 39, cervical cancer is the second leading cause of cancer-related mortality.<sup>14</sup> Xu *et al.*<sup>15</sup> employed metabolomics-based liquid chromatography-tandem mass spectrometry to analyze plasma-free fatty acid profiles in 114 cervical cancer patients, including 40 undergoing concurrent chemoradiotherapy. While palmitic and stearic acid levels decreased post-treatment, most fatty acids, including oleic acid, arachidonic acid, and total n-3 polyunsaturated fatty acids, showed significant increases, indicating complex lipid metabolic changes associated with radiotherapy.<sup>15</sup>

Hepatocellular carcinoma (HCC) ranks fourth in global cancer mortality and is the leading cause of death in cirrhosis. HCC has an extremely poor prognosis, with a mortality rate nearly equal to its incidence rate.<sup>16</sup> Ng *et al.*<sup>17</sup> conducted a prospective study on 47 HCC patients treated with

stereotactic body radiation therapy. Liquid chromatography-tandem mass spectrometry-based metabolomics revealed increased serum fatty acids and glycerophospholipid post-stereotactic body radiation therapy, suggesting radiation-induced lipid metabolic alterations.<sup>17</sup>

In prostate cancer, an analysis of 91 patients demonstrated significant reductions in high-density lipoprotein (HDL) levels post-radiotherapy ( $p = 0.0159$ ).<sup>18</sup> Similarly, Shaikh *et al.*<sup>19</sup> reported decreased TC (224.4 – 150.2 mg/dL) and LDL cholesterol (142.9 – 89.8 mg/dL) levels in 130 breast cancer patients following radiotherapy.<sup>19</sup>

Giskeødegård *et al.*<sup>20</sup> conducted a comprehensive study on 250 breast cancer patients receiving postoperative radiotherapy, utilizing nuclear magnetic resonance spectroscopy to quantify serum metabolites and lipoprotein subfractions. The study revealed reduced esterified cholesterol levels across HDL subfractions, increased free cholesterol levels, and elevated LDL particle numbers, resulting in increased LDL cholesterol and TG levels post-radiotherapy.<sup>20</sup> These findings collectively indicate that radiotherapy induces significant alterations in serum lipid concentrations in cancer patients.

## 3. The impact of blood lipids on radiotherapy

In summary, radiotherapy is associated with fluctuations in blood lipid levels in cancer patients. Next, we will explore how blood lipids influence the efficacy and complications of radiotherapy (Table 2). This exploration will further guide clinicians in managing patients' baseline lipid levels before radiotherapy, reducing radiotherapy-related adverse reactions, and enhancing radiotherapy's therapeutic effect.

### 3.1. The impact of blood lipids on the efficacy of radiotherapy

Dyslipidemia is a common comorbidity in cancer patients and, to some extent, reflects underlying lipid metabolism disorders. Some studies have explored the correlation between blood lipid levels and radiotherapy outcomes in cancer patients, providing a lipid-based perspective for optimizing individualized radiotherapy strategies. In addition, these findings contribute to the development of clinical guidelines for blood lipid management in patients undergoing radiotherapy.

Huang *et al.*<sup>21</sup> conducted a retrospective study on 140 high-grade glioma patients undergoing intensity-modulated radiotherapy. Patients were grouped based on the average levels of TC, LDL, and HDL in peripheral blood serum (pre-treatment and 6-month post-treatment) to explore whether pre-treatment and post-treatment changes in these blood lipid levels affected prognosis. Patients with

**Table 2. The impact of blood lipids on radiotherapy**

Author (s)	Year	Diagnosis	Tumor staging	Sample size	Types of lipids	Effect
Huang <i>et al.</i> <sup>21</sup>	2023	High-grade glioma	Histology grade III–IV	140	TC, LDL, and HDL	Higher pre-treatment serum cholesterol and elevated post-IMRT serum LDL levels are associated with poorer prognosis.
Wang <i>et al.</i> <sup>22</sup>	2019	NPC	Histology grade III–IV	342	HDL-C	Higher pre-treatment HDL-C levels can predict 5-year failure-free survival in NPC patients.
Zhang <i>et al.</i> <sup>23</sup>	2023	NSCLC	Histology grade III–IV	134	TG, TC, and LDL	Low TG, TC, and LDL levels are associated with poorer prognosis in NSCLC patients receiving iRT.
Harima <i>et al.</i> <sup>24</sup>	2021	Cervical cancer	T×N × M0	145	ApoC-II	Patients with pre-treatment ApoC-II levels ≤25.8 µg/mL have a shorter pelvic progression-free survival.
Guo <i>et al.</i> <sup>25</sup>	2021	Rectal cancer	Histology grade II–III	751	ApoA-I	Patients with pre-treatment serum apolipoprotein A-I (≤1.20 g/L) have a higher incidence of adverse reactions to neoadjuvant chemoradiotherapy.
Goldberg <i>et al.</i> <sup>27</sup>	2022	Pediatric cancer	NA	4115	Non-HDL-C	Abnormal non-HDL cholesterol increases the risk of stroke and peripheral vascular disease in patients undergoing radiotherapy.
Cheng <i>et al.</i> <sup>28</sup>	2023	Head-and-neck cancer	NA	694	TC	Hypercholesterolemia is associated with post-radiotherapy carotid artery stenosis.
Wang <i>et al.</i> <sup>29</sup>	2022	ESCC	I-III	355	Serum lipids	Hyperlipidemia increases the incidence of major coronary events after radiotherapy.

Abbreviations: ApoA-I: apolipoprotein A-I; ApoC-II: Apolipoprotein C-II; ESCC: Esophageal squamous cell carcinoma; HDL: High-density lipoprotein; HDL-C: High-density lipoprotein cholesterol; IMRT: Intensity-modulated radiation therapy; LDL: Low-density lipoprotein; NPC: Nasopharyngeal carcinoma; NSCLC: Non-small cell lung cancer; TC: Total cholesterol; TG: Triglycerides.

high pre-treatment TC levels showed significantly worse 5-year survival rates (4.9% vs. 19.6%) and median survival times (23.6 vs. 24.5 months) than those with lower TC levels. Similarly, patients with higher post-treatment LDL had a 5-year survival rate and median survival time of 11.8% and 20.4 months, respectively, while those with lower LDL had a 5-year survival rate and median survival time of 16.7% and 28.4 months, respectively.<sup>21</sup> These findings suggest that high pre-treatment serum cholesterol and high post-treatment LDL concentrations are associated with poorer prognosis. Wang *et al.*'s<sup>22</sup> retrospective randomized clinical study on 400 nasopharyngeal carcinoma patients revealed that high pre-treatment HDL cholesterol levels improved 5-year failure-free survival ( $p=0.017$ ).<sup>22</sup>

In a single-center retrospective study by Zhang *et al.*,<sup>23</sup> 134 patients with stage III–IV non-small cell lung cancer undergoing immune therapy combined with radiotherapy were included, and correlations between pre-treatment blood lipid levels and both overall survival and progression-free survival were analyzed. The results indicated that low levels of TG ( $p=0.0017$ ), TC ( $p=0.0028$ ), and LDL ( $p=0.0330$ ) were adverse prognostic factors for progression-free survival.<sup>23</sup>

In a multicenter prospective cohort study by Harima *et al.*,<sup>24</sup> 145 cervical cancer patients were analyzed for changes in serum biomarkers before and after radiotherapy.

Multivariable analysis revealed that patients with pre-treatment apolipoprotein C-II (ApoC-II) levels ≤25.8 µg/mL had a shorter pelvic progression-free survival compared to those with ApoC-II levels >25.8 µg/mL ( $p=0.023$ ).<sup>24</sup> The study demonstrated that pre-treatment ApoC-II levels can effectively predict the radiotherapy prognosis of patients with locally advanced cervical cancer. However, the conclusions need further validation due to the small sample size and the fact that the study was limited to a Japanese population.

A retrospective study by Guo *et al.*<sup>25</sup> analyzed serum lipids in 751 patients with rectal cancer (clinical stage II–III) who received neoadjuvant chemoradiotherapy followed by surgery. The study considered tumor regression grading (5 – 3) as an indicator of adverse reactions to neoadjuvant chemoradiotherapy. The results found that patients with pre-treatment serum apolipoprotein A-I levels ≤1.20 g/L had a higher proportion of neoadjuvant chemoradiotherapy adverse reactions ( $p=0.003$ ).<sup>25</sup> This indicates that blood lipid levels are associated with the adverse reactions of radiotherapy in rectal cancer patients.

### 3.2. The impact of blood lipids on radiotherapy complications

Abnormal blood lipid levels can lead to a range of diseases, and studies have shown that higher serum TC and LDL cholesterol levels are associated with an increased mortality

rate from cardiovascular diseases, while HDL cholesterol levels are negatively correlated with cardiovascular disease mortality.<sup>26</sup> However, limited studies investigate whether lipid abnormalities affect cardiovascular diseases following radiotherapy.

A cohort study by Goldberg *et al.*<sup>27</sup> assessed lipid levels in 4,115 pediatric cancer survivors who had survived at least 5-year post-treatment to evaluate the prevalence of specific lipid abnormalities and related cardiovascular risks. The results indicated that abnormal non-HDL cholesterol levels increased the risk of stroke and peripheral vascular disease in patients who received radiotherapy ( $p=0.02$ ).<sup>27</sup> A retrospective study by Cheng *et al.*<sup>28</sup> included 694 head-and-neck cancer patients and analyzed the incidence of carotid artery stenosis after radiotherapy, with a follow-up period of 1 – 3 years. Multivariate analysis showed that hypercholesterolemia (odds ratio: 1.82, 95% confidence interval, 0.97 – 3.41,  $p=0.06$ ) was associated with carotid artery stenosis after radiotherapy.<sup>28</sup>

A cohort study by Wang *et al.*<sup>29</sup> analyzed 355 esophageal squamous cell carcinoma patients who received radiotherapy, selecting them from clinical databases. The results showed that the probability of major coronary events in patients without a history of hyperlipidemia was 7.1%. In contrast, in patients with a history of hyperlipidemia, the likelihood of major coronary events was 92.9% ( $p=0.005$ ). This suggests that hyperlipidemia, as a known risk factor for atherosclerosis, increases the incidence of major coronary events after radiotherapy.<sup>29</sup>

## 4. Mechanisms of lipid metabolism disorders on the effects of radiotherapy

In the preceding sections, we have synthesized evidence demonstrating radiotherapy-induced alterations in blood lipid profiles among cancer patients and the consequential effects of dyslipidemia on therapeutic outcomes. However, mechanistic insights into lipid-mediated modulation of radiotherapy efficacy remain conspicuously absent. We posit that blood lipid homeostasis exerts a regulatory influence on radiotherapeutic responses through tumor microenvironment remodeling. Emerging evidence corroborates tripartite interactions between tumor microenvironment dynamics, lipid metabolism dysregulation, and radiation responsiveness. This review systematically collates contemporary discoveries across these interconnected domains, aiming to illuminate strategic pathways for investigating lipid-driven mechanisms in radiotherapy optimization.

### 4.1. Abnormal lipid synthesis

Abnormal lipid synthesis encompasses excessive fatty acid production and disrupted cholesterol synthesis. Sterol

regulatory element-binding protein 1 (SREBP1) serves as a master regulator, critically governing cholesterol synthesis, fatty acid metabolism, and the delicate balance of lipid homeostasis.<sup>30</sup> The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway is critical in promoting the expression and activity of SREBP1 and fatty acid synthase (FASN), fostering heightened lipid synthesis that drives tumor cell resistance to radiotherapy. A comprehensive review by Mousavikia *et al.*,<sup>31</sup> analyzing 27 preclinical studies and five clinical trials on colorectal cancer, underscored the potential of PI3K/AKT/mTOR pathway inhibition to significantly amplify radiotherapy efficacy through mechanistic interference with lipid metabolism pathways.<sup>31</sup> In a groundbreaking study, Li *et al.*<sup>32</sup> performed comprehensive western blot analyses on prostate cancer cells subjected to radiotherapy, quantifying the protein expression levels of PI3K, phosphorylated PI3K, AKT, phosphorylated AKT, mTOR, and phosphorylated mTOR – key signaling molecules in oncogenic pathways. Their findings revealed that targeted inhibition of the PI3K/AKT/mTOR cascade significantly suppressed prostate cancer cell proliferation, triggered apoptosis, and markedly enhanced radiosensitivity.<sup>32</sup> In a pivotal discovery, Jin *et al.*<sup>33</sup> demonstrated through colorectal cancer cell experiments that exogenous cholesterol-induced pronounced radioresistance in malignant cells, underscoring the critical need for minimizing dietary cholesterol intake in patients undergoing radiotherapy. Their groundbreaking research further unveiled that silencing the SREBP1/FASN signaling pathway significantly inhibited colorectal cancer cell proliferation and triggered accelerated apoptosis following radiation exposure.<sup>33</sup>

### 4.2. Ferroptosis and lipid oxidation

Ferroptosis, a distinct form of regulated cell death, orchestrates its lethal cascade through iron-driven lipid peroxidation. When iron overload converges with rampant reactive oxygen species, polyunsaturated fatty acid-containing phospholipids in cellular membranes become vulnerable to relentless peroxidation. This insidious accumulation of lipid peroxides breaches membrane structural integrity, culminating in the catastrophic collapse characteristic of ferroptosis.

Lei *et al.*<sup>34</sup> presented compelling genetic and biochemical evidence to establish a definitive link between radiotherapy and ferroptosis. Their findings revealed that radiotherapy stimulates lipid peroxidation and upregulates *PTGS2* expression, a pivotal biomarker of ferroptosis. Tumor cells exposed to radiotherapy displayed hallmark ferroptotic morphological features, including mitochondrial condensation and heightened membrane density. Crucially, the administration of ferroptosis inhibitors significantly

rescues cell viability post-radiotherapy, demonstrating a markedly superior effect to other regulated cell death inhibitors. Notably, the ferroptotic response was shown to correlate directly with both radiation dosage and fractionation schemes, underscoring its dynamic nature in therapeutic contexts.<sup>34</sup>

## 5. Conclusion and prospect

Blood lipids represent a modifiable factor in cancer treatment, potentially enhancing radiotherapy efficacy through dietary and pharmacological interventions. Studies have shown that oral omega-3 polyunsaturated fatty acids can improve the nutritional status and regulate inflammation markers in lung cancer patients undergoing radiotherapy.<sup>35</sup> Emerging evidence suggests that omega-3 polyunsaturated fatty acids may improve nutritional status and modulate inflammation in lung cancer patients undergoing radiotherapy.<sup>36</sup> Furthermore, some cohort studies have demonstrated that statins can be used in radiotherapy for nasopharyngeal carcinoma, head-and-neck tumors, and chest tumors, reducing the risk of vascular complications, such as stroke and transient ischemic attacks in patients.<sup>37-39</sup> However, the exact mechanisms of how diet and medication regulate blood lipids concerning radiotherapy remain unclear. More extensive, multicenter, randomized controlled trials are needed in the future. Based on the current research, we may attempt to optimize dietary plans by combining patients' blood lipid levels with tumor types to better control lipid levels.

In this review, we discussed the mutual influence between tumor radiotherapy and blood lipid levels and how regulating blood lipids through diet and medication can enhance the efficacy of radiotherapy. Although controlling blood lipids has shown specific synergistic effects in radiotherapy, more extensive clinical studies are still needed to provide evidence for clinical guidelines and expert consensus. The growth characteristics of different tumor types vary, and their lipid demands also differ. Therefore, controlling blood lipids in tumor patients should involve personalized management based on the patient's baseline conditions and tumor type.

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## Conflict of interest

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## Author contributions

*Conceptualization:* Jiahua Lyu

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