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Metabolomics in Radiotherapy: Current Paradigms and Future Perspectives

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Abstract: Over the last 100 years, much advancement has been made towards understanding the hallmarks of cancer and finding an amicable solution for the treatment of cancer. Still, understanding the clinical management of cancer with its increasing incidence in the 21st century poses great challenge. Radiation therapy is one of the significant modalities which remain an important component as far as cancer treatment is concerned. The main goal of the treatment is to prevent the multiplication of cancer cells and further metastasis. Human exposure to ionizing radiation (IR) has a great impact on the metabolic processes in the normal cells and tissues apart from tumor cells. Therefore, analysis of the metabolites in the stress–responsive pathways and generating a multi-metabolite profiles of the personnel having a great potential in the identification of robust biomarkers that help in predicting the radiation toxicology. This facilitates studying in–depth, the molecular response of cells in response to radiotherapy. In this review, we have focused on the active role of metabolomics in studying the post-radiotherapy changes in the patients and the identification of unique pathways that can be targeted to alleviate the harmful effects of radiation exposure.

Keywords: Metabolomics, Radiotherapy, Ionizing radiation, Diagnosis, Treatment, Cancer

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Introduction

Cancer is one of the most severe diseases in the world, with a maximum number of mortalities (Ma and Yu, 2006; Prakash and Upadhyay, 2021). As per, the recent release of the Globocan 2020 survey, the global cancer burden has risen to 19.3 million cases and 10 million cancer deaths (Sun *et al.*, 2021). Cancer is a disease that originates globally but has potential to invade and metastasize to other parts as well (Baskar *et al.*, 2014; Dan *et al.*, 2021). Cancer research and understanding the cancer metabolome has always

been the most fascinating field in the life sciences; there is still a lot to be unveiled (DeBerardinis and Chandel, 2016). For years, it has been known that cancer cells have increased energy requirements that involve reprogramming of the central metabolic process. The altered metabolome of cancer cells plays an integral role to accommodate inappropriate proliferation, metastasis, and invasion (Schiliro and Firestein, 2021). The growing knowledge of the metabolism of tumor cells, whether benign or malignant, has become

the groundwork for tailored cancer therapies (Luengo *et al.*, 2017).

For the past two decades, metabolomics has become an integral part in delineating and identifying potential biomarkers/findings for diagnosis, prognosis and screening of various cancers, by studying thousands of small metabolites, including nutrients, drugs, and signaling mediators present in the metabolome (Yeung, 2018; Tolstikov *et al.*, 2020). It plays an important role in providing critical information about cancer at the molecular and systematic level (Tuli *et al.*, 2021; Singh *et al.*, 2022). Moreover, this knowledge is important in creating personalized treatment and combination therapies (including conventional and new methods) to treat cancer (Jacob *et al.*, 2018; Schmidt *et al.*, 2021). The primary analytical techniques which are used in metabolomics are NMR spectroscopy and Mass Spectroscopy (MS), each having its own pros and cons. How metabolomics techniques (NMR spectroscopy and MS) play an active role in radiotherapy, is the main hallmark of the current review.

Radiotherapy is a conventional method, which uses high-energy particles/waves to treat cancer patients. Radiations (in the form of X-rays, gamma rays, electron/proton beams) work by damaging the DNA strands by breaking them which keeps the cancer cells from growing ultimately leading to cancer cell death (Gazda and Coia, 2007). The main aim of cancer therapy is to prevent the potential multiplication of tumor cells (Baskar *et al.*, 2012). Exposure to ionizing radiations (IR) in humans also affects the normal metabolic processes in cells and organs and induces complex biological responses that intervene with gene and protein expression, leading to deleterious acute and chronic effects; affecting the quality of life of the personnel (Reisz *et al.*, 2014). Thus, it is important to study the metabolite profile of the cancer cell, using analytical metabolomic techniques. It is also of paramount importance to know the potential biomarkers to determine the radiation toxicity, as a result of therapeutic

and non-therapeutic irradiation (Baskar *et al.*, 2012; Yadav *et al.*, 2016; Aggarwal *et al.*, 2021). Therefore, there is a need to understand the therapeutic response to radiotherapy; as it is clinically important (Baskar *et al.*, 2014). The main objective of radiotherapy is to maximize the radiation doses for tumor cells and minimize the effect on the normal cells (Barnett *et al.*, 2009).

NMR-based metabolomics is non-invasive, a non-destructive therapeutic strategy that calculates real-time information at all the stages of cancer (Li and Deng, 2016). It involves the study of transitions between different states of the nucleus under the influence of a magnetic field and differentiates between the qualitative and quantitative information of the metabolome present in cancer vs. normal cells (Sahoo *et al.*, 2020). On the other hand, highly sensitive, site-specific mass spectroscopy-based metabolomics, uses mass to charge ratio to generate profiles from highly ionized metabolites (Liesenfeld *et al.*, 2013). Over the last decade, it has been studied that MS with rapid optimization has achieved femtomolar sensitivity (Nalbantoglu and Amri, 2019). GC-MS metabolomics profiling of samples of interest revealed many differences between healthy and tumor tissue profiles (Beger, 2013). The choice of technique for a specific experiment depends on the available biological sample, the research question of interest, sensitivity and assigned cost (Yadav *et al.*, 2020; Anjali *et al.*, 2021; Rana *et al.*, 2021). Either of the techniques helps to analyze the relationship between the patients' metabolic phenotypes and radiotherapy sensitivity, toxicology, optimal dose, and resistance, in the tissue samples (Spratlin *et al.*, 2009). Thus, a multi-metabolite profile obtained from NMR or MS provides a potential platform for discerning specific biomarkers to predict the radiation toxicology and, also in predicting the off-target effects in the patient that helps in drug designing and personalized medicine to mitigate the harmful effects of the IR (Menon *et al.*, 2016).

Cancer Metabolism:

Cancer metabolism is one of the oldest and major areas of accelerated research for years. This involves the principle of reprogrammed metabolism of cancer cells, and how these alterations support the metastasis and malignant properties of the cells (DeBerardinis and Chandel, 2016). Metabolic reprogramming is considered a hallmark of cancer; this is a term used for the conventional biochemical mechanisms that are suppressed or enhanced in tumor cells in response to tumorigenic mutations (Boroughs and DeBerardinis, 2015). One of the quintessential examples of reprogrammed metabolism is aerobic glycolysis or the Warburg effect (increase in the rate of glucose uptake and production of lactate, in the presence of oxygen and functioning mitochondria) (Liberti and Locasale, 2016). The altered cancer metabolism promotes cell growth, proliferation, survival and angiogenesis (Liberti and Locasale, 2016). The rewired cancer cell metabolism is clinically/therapeutically important, as this can be used for cancer prognosis, diagnosis and as a biomarker for treatment response (Schmidt *et al.*, 2021).

It is observed that altered intracellular and extracellular metabolites that lead to cancer-associated metabolic reprogramming have intense effects on the gene expression, cellular differentiation and the tumor microenvironment (Pavlova and Thompson, 2016; Lyssiotis and Kimmelman, 2017). The cancer-associated metabolic changes lead to up-regulated intake of Glucose and Glutamine to promote and sustain the cancer cell growth and proliferation (Wang *et al.*, 2018), and to substitute the depleted supplies of normal anabolic precursors, cancer cells acquire opportunist ways to utilize necessary nutrients (Keibler *et al.*, 2016). According to experimental studies, the metabolic difference between the normal cells and cancer cells holds potential for anti-cancer strategies, giving it a therapeutic perspective. Tumor cells have a higher rate of catabolic uptake, transfer, and assimilation than normal cells, thus catabolic deprivation can be

exploited therapeutically (Martinez-Outschoorn *et al.*, 2017). Also, targeting glycolysis and mitochondrial metabolism in conjunction with drug combinants can act as another promising anti-cancer strategy (Liberti and Locasale, 2016). As cancer cells have up-regulated metabolic pathways than the normal cells, dose-limited toxicology becomes a challenge in the development of drug targeted therapies in cancer cells; a lot is still to be elucidated and clinically important as well (Baudino, 2015).

Radiotherapy:

For more than 100 years, radiotherapy is an indispensably effective treatment method for cancer. It was the year 1895, when physicist Wilhelm Conrad Röntgen discovered the clinical usefulness of X-rays and presented their role in cancer treatment for the first time (Gianfaldoni *et al.*, 2017). Radiotherapy, alone or in conjunction with surgery or chemotherapy, is an important and cost-effective modality used in cancer treatment (Baskar *et al.*, 2012). As per studies, almost 50% of cancer patients (benign or malignant) benefit from radiation therapy during their course of illness and contribute 40% towards the curative treatment of cancer (Moding *et al.*, 2013; Rosenblatt, 2017). Recent advancements in the field of RT have led to improvements in the therapeutic ratio, as it focuses on more doses to tumor cells than normal tissue, making it clinically critical/important (Koushik *et al.*, 2013).

Radiotherapy treatment involves the use of high-energy ionizing radiations like X-ray, gamma rays, electron beams and protons that affects the DNA strands by creating breaks in the hydrogen bonds (Moding *et al.*, 2013). Radiotherapy works on an ideology that DNA repair capacity is higher in normal cells than the tumor cells (Alhmoud *et al.*, 2020). It prevents the cells from further growth and division; thus, killing the tumor cells. According to the American Cancer Society, unlike chemotherapy and other treatment modalities, RT works on the principle of local treatment, i.e., the treatment is aimed only at the affected tissue/organ, causing more defilement in the

cancer cells than the normal tissues. Though ionizing radiations control the growth of tumor cells (directly or indirectly by killing the tumor cells) but have the potential to cause acute or chronic effects on the normal cells as well (Stone *et al.*, 2003). As per the studies in the past 20 years, a paradigm shift has been seen in radiation therapy and the biological and molecular characteristics related to cellular responses to ionizing radiations (Baskar *et al.*, 2014). The linear energy transfer (LET), total dose, number of fractions and radio-sensitivity of the irradiated cells/tissues accounts for the biological efficacy of radiation (Hall, 2007).

To reduce the effect of radiation toxicity and improve the radiation efficacy and radio-sensitivity, innovative technologies have led to advance alternative techniques like image-guided radiotherapy (IGRT), intensity-modulated radiotherapy (IMRT), stereotactic RT (SRT) and radiosensitizers like gemcitabine, paclitaxel, curcumin etc. (Gong *et al.*, 2021). Advancement in radiotherapy is leading toward the generation of personalized and participative medicine and turning off the ideology of 'one size fits all' (Krzyszczczyk *et al.*, 2019). The potential role of 'omics' in tailoring individual treatment to provide a better outcome of Radiotherapy, by studying the robust biomarkers and potential findings to identify the optimum RT isodose, are some of the key points focused through this article.

Metabolomics:

Metabolomics is the present-day omics technology that involves a comprehensive study of small molecular-weight substances and their interaction in cells, tissues or whole organism (Yang *et al.*, 2019). It employs the art of analytical instrumentation such as nuclear magnetic resonance (NMR) and mass spectroscopy (MS) in concomitance of pattern recognition techniques to study and discover the metabolic changes in the subject of interest (Kim *et al.*, 2008; Beger, 2013). Unlike other 'omics' measures, metabolomics has non-invasive nature and focuses on the basic biochemical activity and the state of cells/tissues

which directly assesses the molecular phenotype; making it an ideal tool for the pharmaceuticals (Kell and Royston, 2014), precision medical care (Jacob *et al.*, 2018), and cancer (Schmidt *et al.*, 2021) among others. Metabolomics defines the final step of omics cascade (Gómez-Cebrián *et al.*, 2019). A classic metabolomics study involves the experimental design, sample collection including serum, cells and tissues that differ between cancerous and non-cancerous groups, metabolome profiling [Mass Spectroscopy (GC-MS, LC-MS) and Nuclear Magnetic Resonance (NMR) Spectroscopy], data analysis, and functional interpretation strategies (Xiao *et al.*, 2012).

Mass Spectroscopy (MS):

The mass spectroscopy technique is one of the significant methods used in the identification and quantification (can quantify even at a lower concentration from femtomolar to attomoles) of the sample metabolome (Nalbantoglu and Amri, 2019). It involves the detection of most of the metabolites based on the mass to charge (m/z) ratio. It is a useful approach; helps both in the identification of disease related metabolites in all the biological samples and in confining the treatment or disease generated molecular patterns from the metabolites (Xiao *et al.*, 2012). It provides greater sensitivity, higher resolution and efficient separation than other analytical techniques (Kowalczyk *et al.*, 2020). MS has high throughput and can detect a large number of traits in one run, and if used in a targeted manner has the potential to be used for large scale clinical studies (Kennedy *et al.*, 2018; Kowalczyk *et al.*, 2020). About 80% of published studies till date account for the usage of LC-MS and GC-MS methods (Emwas *et al.*, 2019). Mass spectroscopy has several applications in cancer treatment, it helps in the development of precision medicine, metabolomic phenotyping, live single cell mass spectroscopy for the identification of circulating tumor cells (CTCs), studying cancer metabolism heterogeneity and complexity, disease progression and other clinically relevant features of tumor

biology (Dettmer *et al.*, 2007; Jacob *et al.*, 2018; Kaushik and DeBerardinis, 2018; Abouleila *et al.*, 2019).

Nuclear Magnetic Resonance (NMR) Spectroscopy:

In the past two decades, NMR has emerged as a crucially important technique other than LC-MS/GC-MS (Emwas *et al.*, 2019). It works on the principle of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy. It is a non-destructive, non-selective technique, which involves easy quantification, high throughput, automatability and reproducibility (Li and Deng, 2016). It is potentially more reliable for large-scale metabolomics as it uses the relatively faster mode of measurement, where all the metabolites in a biological sample can be detected in one run (Emwas *et al.*, 2019). Also, it is highly susceptible to the identification and characterization of compounds that are less amenable through GC-MS/LC-MS (Guennech *et al.*, 2014). Proton-based NMR spectroscopy (^1H NMR) is the one that is employed in most NMR based studies (Dona *et al.*, 2014). It is a mainstream metabolic platform involved in the quantitative analysis and identification of the metabolites present in the biological samples (Gowda and Raftery, 2015). It is extensively used to evaluate the cumulative effect of current and potential therapies, toxicology, optimum dose, radio-sensitivity and radio-resistance and other biological mechanisms (Palmnas and Vogel, 2013). The emerging advancements in the techniques showed a potential role in precision medicine and the development of targeted therapy (Letertre *et al.*, 2021).

Metabolomics In Relation To Cancer Research:

For ages, the reductionist approach has been applied in studying cancer prognosis which involves the separation and identification of contributing factors from the plethora of factors that contribute to the pathologic state (Busso-Lopes *et al.*, 2021). Metabolomics is a critical way of identifying even small changes in protein expressions or structures that help in

understanding significant changes in protein activity and metabolite levels hence, the most sensitive way to study the pathologic state (Schmidt *et al.*, 2021). According to recent studies, metabolomics in conjunction with various molecular biological techniques and other integrative strategies play a significant role in bringing out the molecular underpinning of reprogrammed cancer cell metabolism (Kaushik and DeBerardinis, 2018). It has been used to study the deregulated metabolism and various vulnerabilities in cancer. Reprogrammed metabolism supports the tumor growth and provides a potential source to discover novel cancer biomarkers. Metabolomics research is critical in understanding the complex heterogeneous nature, to study the biochemical pathways involved in cancer for possible targets during the therapeutic intervention (Johnson *et al.*, 2016; Jonsson *et al.*, 2019). It is involved in the development of more sensitive and critical diagnostic methods which help in evaluating the prognostic outcome/early diagnosis and novel therapeutic strategies (Gowda *et al.*, 2008; Gupta and Chawla, 2013).

For decades, many studies have been conducted for the early diagnosis and treatment of tumors, using various detection techniques. Metabolomics help in the identification and validation of metabolic biomarkers that have the potential to diagnose tumor field progression and metastasis in the *in vitro* environment (Han *et al.*, 2021). The potential findings of major metabolome studies in various types of cancers and how it affects various metabolic pathways have been highlighted (Table 1).

Metabolomics can monitor even the smallest changes in the metabolome that occur before the detection of overall phenotypic change that reflects the disease (Kim *et al.*, 2008). The merged analysis of metabolomics and other 'omics' potentially provide more sensitive ways to identify changes related to cancer and discover beyond novel biomarkers (Johnson *et al.*, 2016). Determining the multivariate characteristics of the

Table 1: Summary of metabolites in biofluid samples of various cancer and non-cancer groups using analytical techniques

Tumor Types	Sample	Patients/animal models	Method	Potential Biomarkers/findings	Metabolic pathways	References
Head and Neck squamous cancer cells HNSCC	Serum	Patients with hypopharyngeal cancer (8) after relapse	GC/MS	Metabolites related to glycolytic cycle (Glucose, ribose, fructose) significantly increased and amino acids (lysine, hippurate) decreased.	Glycolysis, amino acid	Yonezawa <i>et al.</i> (2013)
Pancreatic ductal adenocarcinoma (PDAC)	Serum	59 unresectable PDAC patients and 60 healthy patients	LC/MS	4 altered metabolic pathways were potentially associated with PDAC (Linoleic acid metabolism, Glycero-lipid metabolism, Glycero-phospholipid metabolism, Primary bile acid biosynthesis), Increased levels of 4-oxo retinoic acids.	Phospholipid biosynthesis, Bile acid synthesis	Martín-Blázquez, <i>et al.</i> (2020)
Hepatocellular Carcinoma (HCC)	Serum	30 CHB, 29 LC, 30 HCC patients	LC/MS	TCA and 1,2-diacyl-3- β -D-galactosyl- <i>sn</i> -glycerol levels were upregulated while glycyrrhizic acid, 5-hydroxy-6 <i>E</i> ,8 <i>Z</i> ,11 <i>Z</i> ,14 <i>Z</i> ,17 <i>Z</i> -eicosapentaenoic acid was down-regulated as cancer progresses from CHB to LC to HCC, having an imperative role in detecting early-stage prognosis.	TCA cycle and Lipid metabolism	Pan <i>et al.</i> (2021)
Breast cancer (BC)	Serum	152 BC patients	GC/MS	Dimethyldodecane, galactose and α -glycerol stearate in Breast cancer samples were found to be upregulated. Glucopyranoside, tetradecane, mannose and benzene 1,2 dicarboxylic acid levels increase as cancer progresses to different stages.	Glycolysis and lipogenesis	Hadi <i>et al.</i> (2017)
Medulloblastoma (MB)	Cerebrospinal fluid	8 MB patients and 7 patients with neoplastic diseases	MS	Upregulated tryptophan, methionine, serine and lysine in MB patients which support hypoxic conditions	MB associated hypoxia, fatty acid oxidation.	Reichl <i>et al.</i> (2020)

disease is a critical method to establish substantive and predictive metabolomics models for prognosis and prevention (Gowda *et al.*, 2008).

Metabolomics and Radiotherapy:

Radiotherapy is an indispensable cancer treatment modality, which is presently an essential component of cancer treatment, either alone or in a combination of chemotherapy or surgery. Approximately 50% of cancer patients receive radiotherapy as treatment during their course of illness, contributing toward 40% of curative treatment (Baskar *et al.*, 2012). It is observed and analyzed those ionizing radiations induce changes in the metabolite profile of the personnel; mainly affecting the compounds associated with glucose metabolism, phospholipids biosynthesis, and nucleotide metabolism (Crook *et al.*, 2021). As radiotherapy leads to molecular changes at the level of biofluids, it becomes clinically and therapeutically important to incorporate fast and reliable bioassays, to identify potential biomarkers/findings that mitigate the harmful effects of ionizing radiations. Ionizing radiation-induced interventions in the tumor microenvironment (TME) result in functional, stromal and vascular changes at the molecular and cellular levels, and facilitate tumor aggressiveness on recurrence (Barker *et al.*, 2015).

According to clinical studies, the patients undergone RT had higher chances of vascular disease and this determines the radiation-induced morbidity (Russell *et al.*, 2009). According to the American Cancer Society, radiotherapy intervenes with the way the immune system functions, as it decreases the complete blood cell count and increases the rate of infections (Zachariah *et al.*, 2001). Radiation therapy affects the pharmacokinetics of the anti-neoplastic drugs, as it alters the protein and mRNA expressions of drug-metabolizing enzymes and has an indispensable effect on the circulation of the blood and lymphatic system as well as in the hepatobiliary excretion (Chen, *et al.* 2017; Li *et al.*, 2019). Ionizing radiation induced acute or chronic

metabolic oxidative stress generates reactive oxygen and nitrogen species ROS/NOS and contribute to RT-induced cell senescence; as it intervenes with cellular proteins, DNA and phospholipids membrane (Gupta *et al.*, 2020).

Table 2 summarizes the potential findings/biomarkers to assess the radiation induced metabolic alterations on the whole tissue sample of RT undergone patients and non-tumor bearing samples, using metabolomic techniques-Proton Nuclear Magnetic Resonance Spectroscopy (^1H -NMR) and Gas Chromatography Mass Spectroscopy (GC-MS). The findings are therapeutically/clinically important to mitigate the harmful effects of radiation therapy, improve therapeutic results, and optimize non-tumor tissue complications after ionizing radiations.

Conclusion

Radiotherapy with progressive advancement at molecular levels can develop innovative approaches that identify distinctive tumor characteristics and help in more precise target delineation and tracking and optimum isodose delivery. Metabolomics is driven by technology; it is a novel diagnostic discipline based on the ease of use and accuracy involved in comprehensive metabolite evaluation, pattern recognition and statistical analysis. Biomarkers play a huge role in cancer prognosis, and diagnosis and have a strong potential in targeted therapeutics. This field of 'omics' can be elucidated more to characterize a cancer state by identifying significant changes in the metabolite expressions and biochemical pathways. Advancements in metabolomic technology can help in better and early diagnosis of cancer when it is amenable to cure, determine the tumor aggressiveness, and improvement in drug efficacy. The future development and advancement in metabolomics will be dependent on multiple factors including spectral databases of metabolites, linked biochemical identities and their correlation with qualitative assays and validation by metabolic profiles obtained by NMR/MS. Metabolomic studies hold significant potential in identifying multivariate

Table 2: Summary of potential findings observed in the patients during and post radiotherapy

Cancer type	Patients	Sample (Analytical method)	Biomarkers/potential findings	References
Prostate cancer	32 cancer patients underwent PLNRT at 6–time points	Plasma (H–NMR)	A significant increase was observed in the levels of triglycerides and phospholipid metabolites. Lysophosphatidylcholine, the member of group Cephalines, showed increased activity during RT, imposing a higher cardiovascular risk. It suppresses the mitochondrial β -oxidation, as deregulation of acylcarnitines (CAR12:1), (CAR14:1), and (CAR26:0) was observed during and after RT. A decrease in the succinate level, an important intermediate of TCA cycle and initiator of oxidative phosphorylation, was observed after RT. Citrulline, a marker of radiation induced, small bowel toxicity decreased initially but was recovered in 12 weeks.	Ferreira <i>et al.</i> (2021)
Glioblastoma (GBM)	11 patients with GBM at the initial stage of radiotherapy	Serum (GC–MS)	The level of ornithine, tyrosine and urea were reportedly decreased in the metabolome of the serum and in the extracellular region of the Tumor during RT. The Glutamine/glutamate was deregulated in the serum while upregulated during the treatment. The decrease in Glutamate/glutamine level directly affects the ureagenesis, citric acid cycle, amino acid transferase, and lipogenesis. A decrease in the levels of Myo–inositol was observed in the serum and an increase in the extracellular compartment of the tumor during the treatment; becomes a potential for cancer treatment.	Mörén <i>et al.</i> (2016)
Breast cancer	151 women patients who received RT post–surgery	Blood (GC–MS)	Metabolic changes were observed post–RT. RT up–regulated the levels of pyruvate, fumarate, malate, citrate and glutamine. The most important amino acids with metabolic changes were serine, leucine and isoleucine. Concentrations of the important metabolites leucine and isoleucine post RT were significantly less in estrogen–receptor +ve patients than estrogen receptor –ve patients	Arenas <i>et al.</i> (2018)
Hepatocellular Carcinoma (HCC)	47 HCC patients treated with stereo static body radiotherapy (SBRT)	Plasma (GC–MS/ LC–MS)	Higher level of hydroxyl–proline, citrulline and tyrosine after one to two fractions of SBRT was observed. As citrulline is a part of the Urea cycle, up–regulated level of the same indicates an increased load of ammonia and impaired liver function. Up–regulation of Serine and alanine was observed post three months of SBR, hinting towards inadequate mitochondrial compensation and higher protein turnover rate, which might presage to liver toxicology. An increase in amino acids post–SBRT, cause higher protein turnover (increased Hydroxy–proline act as an important biomarker) leading to radiation–induced liver toxicology at a later time. Also, increased expression of fatty acids, glycerophospholipids, and acylcarnitines was observed post SBRT, suggesting early membrane damage and cell death.	Ng <i>et al.</i> (2020)

pathways/biomarkers that can be clinically/therapeutically significant. This review highlights the potential findings/pathways that differ in the cancer cells, and the identification of the biomarkers that are studied to alleviate the harmful effects post–radiotherapy and mitigate the impact of radio toxicity, radio sensitivity, and dosage on the normal cells. The study of

metabolomics and cancer therapy can be used to study the in–depth molecular response of certain drugs, thus encompassing its potential in pharmacokinetics and pharmacodynamics studies. There is a lot to be unveiled, as radiation metabolomics is still in the infancy stage. In summary, there is an immediate need for the development of robust biomarkers that are

clinically relevant and has potential usage in predicting response or no response to radiation therapy and the potential of this approach to involve the implementation of precision medicine in cancer treatment.

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