Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
DOI: 10.29261/pakvetj/2025.124

REVIEW ARTICLE

Non-Invasive Radiographic Techniques in Diagnosing and Treating Malignant Tumors in Animals and Humans: Current Trends and Future Directions

Faisal Alshomrani*

Department of Diagnostic Radiology Technology, College of Applied Medical Science, Taibah University, Madinah 42353, Saudi Arabia
*Corresponding author: fshomrani@taibahu.edu.sa

ARTICLE HISTORY (25-040)

Received: October 24, 2024
Revised: January 28, 2025
Accepted: January 29, 2025
Published online: March 17, 2025

Key words:
Alternatives
Conventional therapies
Diagnosis
Metastasis
Modern radiography
Treatment

ABSTRACT

Non-invasive radiographic techniques have emerged as essential tools in detecting, diagnosing, and treating malignant tumors in humans and animals. These techniques provide precise and accurate therapeutic responses with minimum side effects compared to surgical and conventional techniques. This review article focuses on advanced techniques including proton beam therapy, heavy ion therapy, high-intensity focused ultrasounds (HIFU), intensity modulation radiotherapy (IMRT), and image-guided radiotherapy (IGRT) and their effective and targeted use against superficial and deep organs including brain, bone, breast, liver, spleen, prostate and renal tumors in both humans and animals. These techniques are very effective and accurate in tumor destruction while minimizing damage to healthy tissues. Their effectiveness is enhanced when combined with advanced imaging techniques and other chemotherapeutic drugs. During the past decades, the application of modern radiographic techniques has been growing globally and frequently expanding for the treatment of various malignancies. However, due to cost-effectiveness and a very complicated structure, these therapies are not easily approachable. The effectiveness of these techniques can further be modified by using nanotechnology, artificial intelligence, and machine learning to make it more precise and economical.

To Cite This Article: Alshomrani F, 2025. Non-Invasive radiographic techniques in diagnosing and treating malignant tumors in animals and humans: Current Trends and Future Directions. Pak Vet J, 45(1): 48-61. http://dx.doi.org/10.29261/pakvetj/2025.124

INTRODUCTION

Malignant tumors are cancerous growths characterized by uncontrolled and abandoned cell divisions in humans and animals (Chen *et al*., 2024; Kasperski and Heng, 2024). Malignant cells are less differentiated than normal cells and they can invade nearby cells and tissues through a process known as metastasis (Gerstberger *et al*., 2023; Ambrose *et al*., 2025). These less differentiated cells can interrupt the normal body metabolism (Yao *et al*., 2021) and are classified based on the origin from which they are derived (Choi and Ro, 2021). For example, carcinomas instigated from epithelial cells include adenocarcinoma (glandular tissues), and squamous cell carcinoma (skin or lungs) (Zhu *et al*., 2023; Shen *et al*., 2024). Similarly, sarcomas developed from connective tissues include osteosarcoma (bone), myeloma (muscle), and liposarcoma (fat) (Hou *et al*., 2019; Crombé *et al*., 2024). Leukemias (acute lymphoblastic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia) and lymphomas (Hodgkin lymphoma and non-Hodgkin lymphoma) are cancers of blood and bone marrow, respectively (Amin *et al*., 2023; Vijayakumar *et al*., 2024). Furthermore, tumors called melanomas originate from melanocytes (pigment-producing cells) in the skin and eyes, brain tumors (gliomas), spinal cord (meningioma) can occur in both humans and animals (Galbraith and Snuderl, 2024; Valdez-Salazar *et al*., 2024).

In humans and animals, the number of cases of cancer is markedly growing in developing countries where there are fewer opportunities for early detection and treatment (Mamun *et al*., 2024). Every year, almost 12-13 million people and 20-25 million animals are diagnosed with cancer (Eissa *et al*., 2024). In developed countries, it has become the leading cause of death, but in developing countries, it is the second most common cause of death after heart disease (Boire *et al*., 2024; Marino *et al*., 2024). At older age, the risk of cancer in developed countries reaches up to 78%, while it is less in developing countries (Nolen *et al*., 2017; Bourgeois *et al*., 2024). In the United States, in 2024, two million new cases of cancer and 0.61 million deaths have been reported (Islami *et al*., 2024). In European countries, including the United Kingdom, 2.17 million deaths due to cancer have been recorded, and the majority of deaths were due to lung cancer, prostate cancer, and breast cancer (Gao *et al*., 2024a). It has also been observed that the ratio of incidence and prevalence in males is more than in females. Similarly, in China, 4.5 million new cases and 2.9 million deaths due to cancer have been reported, which accounts for 25 and 30% of the global account (He *et al*., 2024). Furthermore, in South Asian countries (India, Pakistan, Sri Lanka, Bangladesh, and Nepal) 1.7 million new cases and 1.1 million deaths have been reported in 2020 (Virani *et al*., 2024).

Cancer in animals causes significant economic losses in farm and companion animals (Efird *et al*., 2014). For farm animals, it reduces the production of eggs, meat, milk, and hide (Bahrami and Tafrihi, 2023). While the cancer of reproductive organs leads to infertility and culling of the animals. Resources are further strained by veterinary expenses, which include diagnosis, treatment, and aftercare. Livestock malignancies also reduce market value, interfere with trade, and require expensive carcass disposal (Clemmons *et al*., 2021). The financial strain also extends to expenditures in prevention and treatment. For instance, Marek's disease in poultry and mammary cancers in dairy cattle have a major influence on productivity, whereas companion cancer cures in the US cost billions of dollars per year (Munson and Moresco, 2007; Prasad *et al*., 2024).

Addressing these losses requires prioritizing early diagnosis, preventive measures, and effective management strategies. Cancer has a significant financial impact on people, animals, and healthcare organizations because of treatment costs, diminished productivity, and the requirement for long-term care (Nanayakkara *et al*., 2021). Diminished productivity due to the tumor arises as patients often experience fatigue and pain, which in turn reduces their ability to work effectively and efficiently. For this purpose, invasive (ambulatory surgery) techniques have played an important role in the early diagnosis and treatment of cancer, offering a direct approach to removing cancerous growth (Stone *et al*., 2021). These methods are often considered when tumors are localized and can be exercised without damaging the healthy area (Tohme *et al*., 2017; Pak *et al*., 2020). On the other hand, surgical techniques may lead to severe complications including infections, excessive bleeding, organ damage, pain, emotional disturbance, spread to other organs, and long recovery time (Wills and Obermair, 2013). So, surgeons and researchers divert their attention toward non-invasive techniques due to their significance in modern medicine, which has minimum risk and quick recovery (Imam, 2021). In this review, our focus is to discuss non-invasive radiographic techniques and their mode of action in treating malignant tumors with their current trends and future challenges.

Factors associated with tumor development and its geographical distribution: Various factors including hereditary and environmental factors encouraged the growth and development of malignant tumors (Sawicki *et al*., 2021; Borja *et al*., 2024). Environmental factors include chemical carcinogens (tobacco, industrial chemicals, pesticides, herbicides, aflatoxins), physical carcinogens (ultraviolet radiations and ionizing radiations), biological carcinogens (viruses, bacteria, parasites), lifestyle (diet, physical inactivity, substance abuse), environmental pollution (air, water and soil pollution), occupational exposure (copper, lead, and asbestos), and hormonal disruptors (bisphenol A and phthalates) (Protano *et al*., 2021; Schiller and Lowy, 2021; Kobets *et al*., 2022; Goswami *et al*., 2024). A case-control study was conducted on 800 participants, which included 400 colorectal patients and 400 controls to assess the risk factors. The result data revealed a strong positive relationship between ulcerative colitis, smoking, obesity, lack of physical activity, and high fat or red meat consumption with an increased risk of colorectal cancer. Smokers had a 2.17 times higher risk, while obese individuals had 1.27 times higher risk as compared to non-smokers and non-obese (Lewandowska *et al*., 2022). Another study conducted by Giannandrea and Fargnoli (2017) confirmed that testicular cancer in children is due to poor diet and nutrition, inadequate lifestyle, domestic and occupational exposure to pesticides, and exposure to harmful chemicals present in the environment. In the United States, almost 6 persons out of 100 die each year due to occupational exposure (Boice *et al*., 2024). Furthermore, cancer chances in the aged population have also increased due to their weak natural immunity and greater genomic instability (Berben *et al*., 2021). Fig. 1 shows various genetic and environmental factors that are involved in the growth and development of cancerous cells.

Researchers have shown that the forms of cancer detected globally vary significantly by geography (Laguna *et al*., 2024). These distributions in cancer occurrence result from differences in the average age of people, the frequency of key risk factors, and both the type and level of complexity of cancer screening and medical care (Bortty *et al*., 2024). In the past few decades, it was confirmed that 15% of cancers in males (stomach and liver) and females (cervix) are due to chronic bacterial or viral infections, and the ratio is higher in developing countries than in developed countries (Kuper *et al*., 2001). The greatest variation of cancer types, including lung, liver, Kaposi sarcoma, and non-Hodgkin lymphoma, has been observed in Africa (Parkin *et al*., 2020). Similarly, lung, thyroid, and liver cancers are more prevalent in China, South Korea, and Vietnam, respectively (Luo *et al*., 2021; Choi *et al*., 2022; Ha *et al*., 2023).

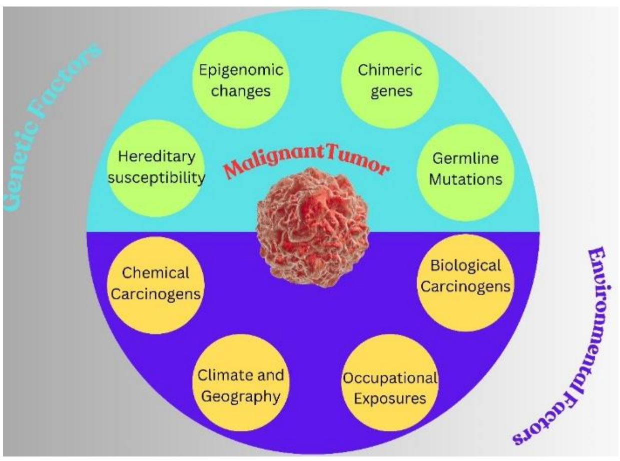

Fig. 1: Genetic and environmental factors associated with the development of malignant tumors.

Treatment of tumors by non-invasive radiographic techniques: Non-invasive radiographic techniques for malignant tumors are advanced therapeutic approaches that inhibit or destroy the tumor growth without performing any surgical incisions. These techniques used precise energy-based modalities, including photon or proton beam therapy, ultrasound, and radiation, to target and destroy tumor cells without causing damage to nearby healthy tissues (Beniwal *et al*., 2024). Additionally, these techniques have increased the accuracy of tumor diagnosis at early stages and overall improved patient outcomes. They are helpful in the treatment of various tumor types, neurological disorders, and chronic pain. Furthermore, they have less recovery time, shorter hospital stays, reduced pain, and often have lower healthcare costs (Braga, 2015). For malignant tumors, non-invasive techniques are better options for those patients who are very unable to afford surgery due to their ages, pain, and other health problems (Qiu *et al*., 2023). Non-invasive techniques are categorized into conventional (radiation therapy and endoscopy) and modern therapies (high-intensity focused ultrasound, MRI-based high-intensity focused ultrasound, and image-guided radiation therapy) (Kumari *et al*., 2021; Ali *et al*., 2024). Some of the conventional and modern non-invasive radiographic techniques are given in Fig. 2.

The non-invasive conventional radiographic techniques: Conventional non-invasive radiographic techniques are imaging protocols that use electromagnetic waves, radiations, and rays to visualize the internal body structure without any surgical incision. These protocols are frequently used in medical diagnosis for detecting various types of tumors, abnormalities, and sometimes injuries. These techniques include thermal ablation (cauterization and diathermy) (Rao and Kumar, 2014), cryotherapy (Theodorescu, 2004), radium therapy (Humm *et al*., 2015), laser therapy (Dowlatshahi *et al*., 2002), brachytherapy by radium beads and needles (Skowronek, 2017) and X-ray radiography (Warmuth *et al*., 2010). These conventional techniques present various benefits in medical diagnosis and treatment because they are painless, efficient, quick, and allow precise and accurate tumor detection without surgical intervention. These are widely available and cost effective compared to advanced imaging methods. No doubt, they are very effective for treating malignant tumors, but these techniques can cause serious problems for the healthy tissues (Hall and Brenner, 2008). For example, less precise cauterization and cryotherapy can damage the nearby healthy areas and lead to a delayed healing process. They are also painful procedures with post-operative inflammation, which can lead to severe infection (Buckley, 2012). Furthermore, improper technique and excessive use of heat and cold can cause cellular injury and there are more chances of recurrence of abnormal growths (Habash *et al*., 2007). During radium therapy, the emission of different radiations, including α, β, and γ can harm healthy tissues as well and increase the risk of secondary growth tumors. Due to the toxic nature of radium, it can also pose threats to patients and medical personnel during handling and disposal (Ray and Stick, 2015). Furthermore, the penetration ability of radium to the tumor cells is less, so it is less effective for tumors that are located in the deep tissues (Asadian *et al*., 2020). Radium therapy, once a cornerstone of radiographic cancer treatment, has largely been replaced by modern radionuclide-based therapies such as lutetium-177 and iodine-131, which offer greater specificity and lower systemic toxicity. Similarly, brachytherapy needs surgical incision to place radioactive substance near the tumor site that leads to pain, inflammation, and severe bacterial or viral infection (Helou and Charas, 2021). High-dose brachytherapy (HDBT) can also lead to the exposure of associated normal cells and tissues. Although HDBT increases radiation exposure risks, it also enables localized high-precision treatment, reducing systemic side effects compared to external beam radiation therapy (Logghe *et al*., 2016). These techniques have been widely employed in malignant tumor treatment; however, their efficacy varies depending on tumor type, stage, and location (Albano *et al*., 2021; Brook, 2021). Some of the old non-invasive radiographic techniques used in the treatment of malignant tumors in humans and animals with their possible effects and limitations are elaborated in Table 1.

Modern non-invasive techniques in treating malignant tumors: Modern non-invasive procedures for the treatment of malignant tumors have created a revolution in cancer therapy by providing effective and targeted treatment with minimal harm to the surrounding normal cellular tissues (Gromek *et al*., 2024; Pereira *et al*., 2024). These procedures, along with precision medicine, are reshaping cancer cells by reducing pain and long-term complications, improving patients' outcomes and quality of life. Despite their advantages, these modern radiographic techniques also present challenges, such as high operational costs, limited availability in certain regions, and potential radiation-related risks that require further investigation (Jones *et al*., 2023). Currently, various modern and effective radiographic techniques, including proton beam therapy, heavy ion therapy, HIFU, IMRT, IGRT, and magnetic resonance-guided radiotherapy (MRgRT), have been used to treat malignant tumors. Different techniques are suited for different types of malignancies. For instance, proton beam therapy is particularly beneficial for pediatric cancers due to its ability to minimize radiation exposure to healthy tissues, whereas HIFU has shown promising results in treating prostate and kidney tumors (Smith *et al*., 2022). While techniques such as MRgRT and IGRT have been successfully integrated into clinical practice, other approaches like heavy ion therapy remain largely restricted to specialized research centers (Lee *et al*., 2024). These techniques with their mode of actions are described below.

Proton beam therapy: Proton beam theory (PBT) is a sophisticated and extremely focused type of radiation therapy that uses protons, positively energized particles, to accurately target and eliminate tumor cells (Mohan, 2022; Fairweather *et al*., 2024). This method sets itself apart from conventional photon-based radiotherapy by providing greater dose of distribution and allowing high-dose radiation to be delivered directly to the tumor while drastically lowering radiation exposure to nearby healthy tissues (Paganetti *et al*., 2021b). PBT is especially helpful for treating tumors that are close to delicate or important structures, like those in the brain, spinal cord, or head and neck areas, because there is little to no radiation exposure after this point. This high degree of accuracy improves patients' quality of life by minimizing harm to important organs and lowering the possibility of adverse treatment effects (Matsumoto *et al*., 2021).

The Bragg peak, a special physical characteristic of protons, is essential to PBT's efficacy. The radiation dose rapidly decreases beyond this depth, thereby preventing exposure to tissues outside the target area (Newhauser and Zhang, 2015). In one of the clinical studies, the effect of PBT on muscle growth in 17 pediatric patients was examined. The results confirmed that muscle growth is significantly reduced on the irradiated side (>50 Gy) as compared to the irradiated side (Nitta *et al*., 2024). In a similar study, the effect of PBT was evaluated on patients having hepatocellular carcinoma, and results showed shrinkage of the tumor with higher response rates at 6, 12, and 24 months (Niitsu *et al*., 2024). Overall, the studies concluded that patients treated with PBT have better survival rates, and proper monitoring and continuous sessions will reduce the growth of the tumors. Recent study confirmed that integration of PBT with advanced imaging technologies may further improve the treatment planning systems (Alterio *et al*., 2024).

To create detailed three-dimensional models of the tumor and its surrounding anatomy advanced imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans, are used that allow clinicians to develop a highly individualized treatment plan (Burnet *et al*., 2020; Gao *et al*., 2024b). These imaging modalities help determine the tumor's exact size, shape, position, and proximity to vital organs. This feature allows high-dose radiation to be confined to the tumor while sparing surrounding healthy tissues and critical structures (Ying *et al*., 2024). Furthermore, the proton beam can be precisely shaped and modified to fit the contours of the tumor using pencil beam scanning, a state-of-the-art delivery technique (Ebadi *et al*., 2024). This feature guarantees that cancers in difficult-to-treat locations or with unusual shapes can be successfully treated (Padilla-Cabal *et al*., 2018). Modern treatment planning combined with the physical characteristics of the Bragg peak highlights PBT's ability to enhance therapeutic results while reducing toxicity (Ragavendran, 2024).

Currently, PBT, along with other associated imaging techniques is used to treat various tumors. For example, PBT has been shown to be significant in controlling secondary glioblastoma, a rare but extremely aggressive brain tumor that arises in people treated with radiation treatment for other tumors. PBT technique was selected because of its accuracy and capacity to deliver a high dose directly to the tumor while minimizing the dose to surrounding healthy tissue. The patient received proton beam therapy that targeted the tumor bed and concurrent chemotherapy. The outcomes were encouraging and the patient had a tolerable degree of side effects, and the tumor reacted to the treatment by regressing (Jiwei *et al*., 2024).

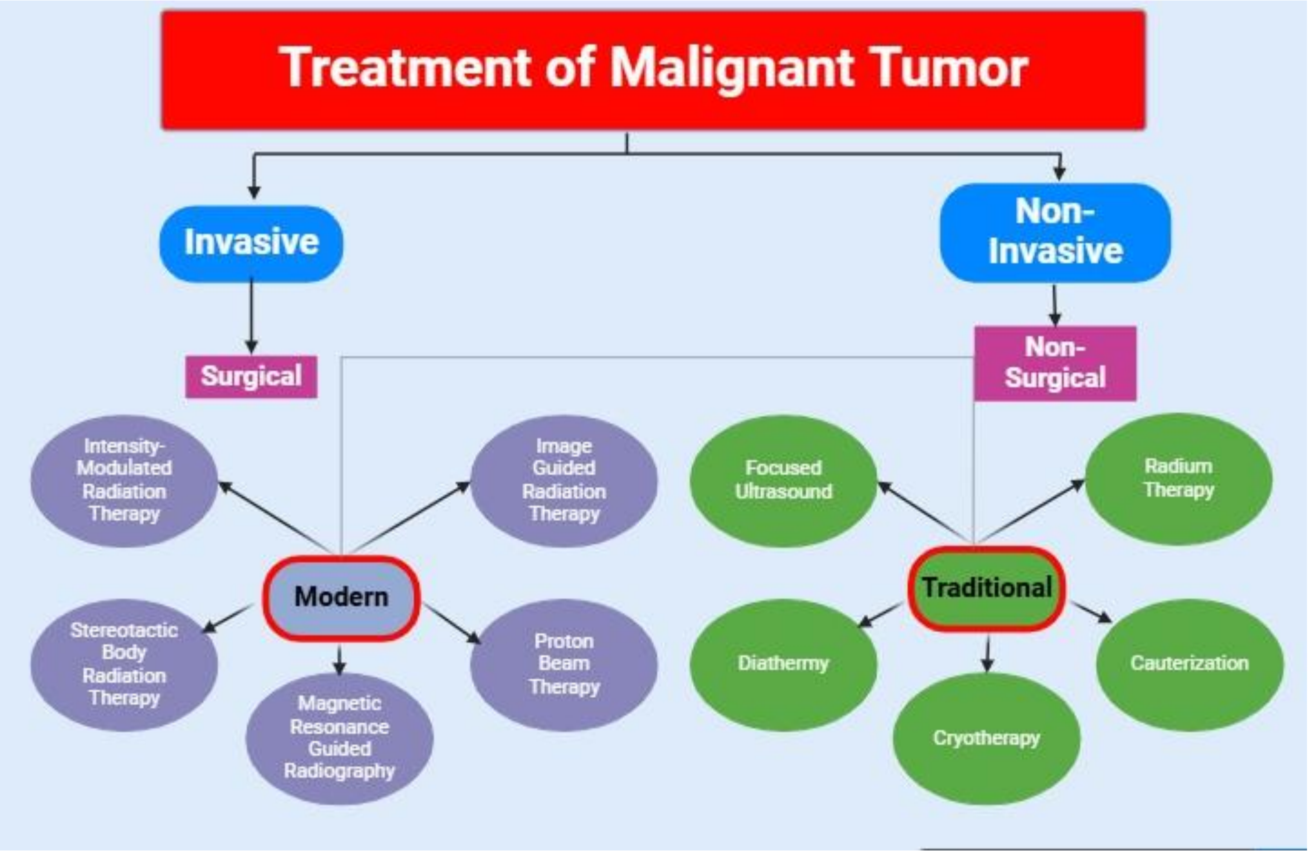

Fig. 2: Conventional and modern radiographic techniques used for the diagnosis and treatment of malignant tumors. The source of Fig is (www. Biorender.com).

Table 1: Non-invasive conventional radiographic techniques for the treatment of malignant tumors and their possible outcomes and limitations

Technique name	Types	Method	Dose rate	Application in malignant tumors	Tumor of a specific organ	Species	Possible outcome (Effectiveness)	Limitations	References
Cauterization	Thermal cauterization	Heat through the metal probe	50-100°C	superficial tumors	Skin, breast, prostate	Humans and animals	surface tumors	Healthy tissue damage	(Stauffer and Goldberg, 2004)
	Radiofrequency cauterization	High-frequency waves	300-500 kHz	Internal organ tumors	Kidney, liver	Only humans	Minimally invasive	Limited to specific tumors	(Pace-Asciak *et al.*, 2022)
	Cold cauterization	Cold probe or gas	-20 to -100°C	Early-stage tumors	Skin, breast, cervical	Humans and animals	Less pain and bleeding	Not for systemic tumors	(Shinozaki *et al.*, 2018)
Cryotherapy	Liquid nitrogen cryotherapy	Cryoprobe	-20 to -50°C	Early-stage and localized tumors	Bone, musculoskeletal, breast, prostate, cervical, liver, kidney, and skin tumors	Humans and animals	Safe for sensitive areas, fewer side effects	Feer recovery times. Not effective for systemic tumors	(Baust *et al.*, 2014; Chen *et al.*, 2017; Ciambella and Takabe, 2024)
Diathermy	Microwave diathermy	Microwave radiations	915 MHz to 2.45 GHz	Deep tumors	Liver, lungs, and bone metastasis	Humans and animals	Destruction of deep tumors, pain relief, short recovery time	Limited depth, not effective for irregular shaped tumors and advanced-stage tumors	(Machado *et al.*, 2017)
	Ultrasound diathermy	High-frequency acoustic waves	1 to 3 MHz	Soft and superficial tissue tumors and	Prostate, breast, and pancreatic	Humans and animals	Enhanced blood vascular permeability and circulation	Not effective for deep tumors or tumors located near critical organs,	(Marchal *et al.*, 2019)
	Capacitive diathermy	Electrodes are used	13-27 MHz	Superficial and small tumors	Skin cancers and superficial lesions	Humans and animals	Enhanced blood circulation and enhanced drug delivery	Ineffective for large and deep tumors, not effective for advanced-stage tumors	(Lara-Palomo *et al.*, 2024)
	Inductive diathermy	Magnetic fields alternate with electric fields	27 MHz	Deeper tissues tumors	Musculoskeletal tumors (bone and cartilage)	Only humans	Increased blood circulation, enhanced oxygenation, reduced tumor size, reduced inflammation	Burns, healthy tissue damage, not effective for advanced-stage tumors, tumor recurrence	(Parise and Cristina, 2009; Oleson, 2019)
Laser therapy	CO_2 laser	Infrared rays of 10.6 µm absorbed by water in tissues and cells	Low to medium	Skin and superficial tumors	Basal cell carcinoma, squamous cell carcinoma, vocal cord tumors, penile and bladder tumors	Animals and humans	Coagulation effect to prevent bleeding, tumor necrosis, and precise cutting	Ineffective for deep-seated tumors, recurrence of tumors	(Rucci *et al.*, 2010; Soleymani *et al.*, 2017)
	Diode laser	Emission of visible and near-infrared region waves	810 to 1100nm	Skin and superficial tumors	Basal cell carcinoma, squamous cell carcinoma, vascular tumors, vocal cord tumors, penile and bladder tumors	Animals and humans	Cause thermal coagulation and vaporization of tumor cells	Ineffective for deep organ tumors, chances of recurrence	(Karkos *et al.*, 2021)
	Argon laser	Gas laser emission	Low to medium (480-514.5nm)	Skin and superficial tumors	Retinoblastoma, esophageal tumors, conjunctival tumors, basal cell carcinoma, and squamous cell carcinoma	Humans and animals	Hemostasis, thermal coagulation, target	Localized tissue effects, edema, erythema, hypopigmentation and hyperpigmentation, ocular abnormality	(Cui *et al.*, 2022; Han *et al.*, 2022)
Brachytherapy	Permanent seed brachytherapy	Iridium-192, Iodine-125, palladium-113 are placed at tumor site	Low energy	Deep tissue	Prostate, brain, and breast cancer	Humans and animals, especially canines	Direct damage to DNA, cell cycle arrest	Seed migration during implantation, collateral damage to healthy tissues, complex method	(Lim and Kim, 2021; Cozzi *et al.*, 2022)
Hormonal ablation	Targeted hormonal therapy	Monoclonal antibodies block or reduce tumor growth	8mg/Kg	Superficial and deep-seated tumors	Breast, prostate, lungs, liver, kidneys, ovarian, and renal cell carcinoma	Humans and animals	Target HER2 receptors, reduced tumor size	Hormonal resistance, hot flashes, bone resorption and osteoporosis, cardiovascular risk	(Zoubeidi and Ghosh, 2021)
Conventional X-ray therapy	-	X-rays	20-60 Gy	Superficial tumors but sometimes deep tumors	Breast, prostate, ovarian, and renal cell carcinoma, squamous cell carcinoma	Humans and animals	Generate photoelectric effect, DNA breaks of tumor cells, and partial reduction of tumor cells.	Damage to skin, skin rashes, irritation	(Karkos *et al.*, 2021)

Notably, PBT helped lower the long-term hazards of additional radiation exposure, including neurological damage and cognitive impairments, which are frequent adverse consequences of conventional radiation therapy on previously exposed brain tissue (Paganetti *et al*., 2021a; Hudson *et al*., 2024). The most prevalent malignant brain tumor in children is medulloblastoma, which was frequently treated with craniospinal irradiation (CSI) by using proton beams to target the main tumor as well as possible metastases. A comparative study was conducted to compare the effects of conventional photon-based methods with PBT while treating medulloblastoma in children. Forty-three children having medulloblastoma were divided into two groups. Half of the patients were given proton radiotherapy combined with CSI while the other half group was exposed to conventional photon beams. Results have shown a favorable toxicity profile with better tumor control and less harmful effects for the group treated with proton therapy (Kahan *et al*., 2023).

No doubt, surgical resection is still the major therapeutic option to treat ameloblastic carcinoma, but ameloblastic carcinoma is difficult to treat because of its aggressiveness, high recurrence rate, and closeness to important head and neck tissues (Niu *et al*., 2020). In one of the studies, PBT and retrograde intra-arterial chemotherapy were chosen in order to minimize harm to nearby healthy tissues and optimize tumor control. It is advantageous because the ability of proton beam therapy to precisely administer high radiation doses to the tumor while preserving adjacent vital structures. In another study, PBT combined with retrograde intra-arterial infusion chemotherapy was used to treat a patient with ameloblastic carcinoma of the maxilla. The goal of the retrograde intra-arterial chemotherapy was to decrease systemic toxicity while increasing therapeutic impact by delivering cytotoxic chemicals straight to the tumor via the blood supply. The patient's tumor significantly shrank after the course of treatment, and follow-up imaging verified that there was no disease left behind (Ikawa *et al*., 2024). In addition to producing positive tumor control results, the combination treatment method produced tolerable side effects such moderate mucositis and temporary xerostomia that went away with time (Gaikwad *et al*., 2024). The precision of proton therapy combined with targeted chemotherapy delivery may offer a more effective and less invasive substitute for managing this rare and challenging malignancy (Tubridy *et al*., 2024).

PBT can improve treatment compliance in patients with upper gastrointestinal (GI) cancers as shown by recent clinical studies. Patients are more likely to tolerate higher doses of radiation and finish the prescribed treatment regimen. By lowering the incidence of severe side effects, PBT reduces long-term complication like fibrosis, GI perforation, and liver dysfunction (Srinivasan *et al*., 2024). In pediatric oncology PBT is being used more and more, where it is crucial to preserve developing tissues (Nitta *et al*., 2024). Other than its effectiveness one primary challenge is that it is highly expensive with expensive infrastructure with limited accessibility to the patients (Mohan and Grosshans, 2017). Additionally, PBT is only effective in the treatment of localized tumors with poorly defined borders. At the end, the availability of PBT for tumor patients depends upon the expert and specialized clinicians that are making it rarer.

Heavy ion therapy: Heavy ion therapy is an advanced procedure that uses accelerated heavy charged particles that are heavier than helium ions and have relatively high biological effectiveness (RBE) against malignant tumors (Durante *et al*., 2021). Among heavy ions, carbon-charged ions offer greater dose distribution and biological effectiveness against X-ray-resistant tumors (Yamada *et al*., 2021). Carbon ions released from heavy accelerators form Bragg's peaks (high-energy peaks) that target specific and deep areas of malignant tumors without causing damage to nearby tissues and organs (Hamad, 2021).

Carbon ion radiotherapy (CIRT) is very effective against deeply located tumors and was first used in Japan in 1994 against tumors present in neck and head tumors (Okada *et al*., 2010; Demizu *et al*., 2021). Later on, it was used to treat skull, spine, lungs, liver, pancreas, prostate, bone, and soft tissue sarcomas (Matsumoto *et al*., 2013; Makishima *et al*., 2019; Light and Bridge, 2024). In one of the research studies, the effect of CIRT was examined on 35 patients having hepatocellular carcinoma (HCC). The study evaluated the safety and efficacy of CIRT for HCC with control and survival rates of 76.55 and 69.4%, respectively, and no significant liver function deterioration was observed (Shibuya *et al*., 2022). In another study, CIRT was performed on 53 patients having bone sarcoma. The study revealed that after a follow-up of 36.9 months, the overall survival rate, control rate, and progression-free survival rates were 79.9%, 88.6%, and 68.9%, respectively, with no higher acute toxicities. Some of the patients experienced radiation dermatitis and osteomyelitis (Shiba *et al*., 2021).

Heavy ions having high linear energy transfer (LET) have more genotoxic and cytotoxic effects. Heavy exposure of the ionizing radiations causes changes in cellular structure such as irregular projections, cell membrane invagination, distension of sarcoplasmic reticulum and increased number of autophagic vacuoles (Talapko *et al*., 2024). These alterations cause cell death due to necrosis, apoptosis, delayed cell growth, premature deterioration, autophagy, and enhanced maturation process (Zheng *et al*., 2024). Carbon ions also have the ability to kill cells at cell cycle stages, including the resting phase, prophase, metaphase, anaphase, and telophase. In one of the studies, it was confirmed that carbon ions target radioresistant tumors by causing mutation in the tumor suppressor gene TP53, and they also cause overexpression of the BCL-2 (also known as Bcl-2) cancerous genes (Hamada *et al*., 2008; Sudo *et al*., 2024).

No doubt carbon ions alone are very effective in killing tumor cells, but their efficiency can be increased when they are used in combination with other chemical agents. In one of the studies when carbon ions are given with Bcl-2 inhibiting drugs (docetaxel and halogenated pyrimidine), they cause hyperthermia and also target tumor cells more efficiently (Kitabayashi *et al*., 2006). The tumor control rates by CIRT were remarkable when one of the studies confirmed its control rate more than 80% against adenoid cystic carcinoma and mucosal carcinoma in the head and neck regions (Castello *et al*., 2018). In another study conducted by Hu *et al*. (2021) confirmed the efficacy and safety of CIRT when combined with IMRT. The study was conducted on 69 patients having non-metastatic nasopharyngeal carcinoma with a follow-up of 31.9 months. Overall survival rate and progression-free survival rates were calculated, which were 94.9 and 85.2% respectively, with minimum toxicity to the surrounding tissues. Similarly, in another study, it was confirmed that the tumor control rate of CIRT against early-stage lung cancer was more than 90%, and they have shown promising results against critical organs, including pancreatic and liver cancer cells (Seneviratne *et al*., 2022).

Nowadays, clinicians are using iodine and gadolinium as heavy ions and contrast agents in MRI and CT scan to enhance the visibility of tumors (Ahmad *et al*., 2023). These studies suggest that CIRT alone or in combination with other techniques is a promising tool for improving the systematic control of tumors while maintaining a favorable safety profile. On the other side the potential threats of heavy ions cannot be ignored because they are also involved in the production of secondary growth areas. No clear evidence for the production of secondary tumor cells has been observed, but a series of experiments has been carried out on gland tumors of mice and confirmed the induction of secondary growth areas (Andreucci *et al*., 2014). This technique is also not used globally because of its complexity and heavy expenditure.

High intensity focused ultrasound: HIFU has been studied and used as a therapeutic technology in various experimental laboratories over the last few decades (Quadri *et al*., 2018). Normal diagnostic ultrasounds have frequencies and intensities in the range between 2-16 MHz and several hundreds of mW/cm2, respectively (Polańska *et al*., 2021). HIFU has the ability to emit rays of more than 300 kHz to several MHz that target specific areas of the tumor (Ellens and Hynynen, 2023). Moreover, HIFU targets specific areas and volumes of tumor cells with intensities of more than 1500 W/cm2 and causes ablation of the targeted area (Yoo, 2018). HIFU causes tissue necrosis by generating a high temperature of more than 80°C, which causes the localized and fast death of tumor cells in seconds (Ashar and Ranjan, 2023). The significance of this procedure lies in the fact that due to short exposure time, there are fewer chances of tissue damage to nearby cells. On the other side, HIFU causes the death of tumor cells by producing cavitation (tiny bubbles in the tissues) (Hu *et al*., 2023). Cavitation through HIFU produces mechanical stress and thermal damage that will lead to tissue death. This phenomenon is quite different from the histotripsy because in histotripsy cavitation produces only mechanical stress and does not produce thermal effects (Xu *et al*., 2024).

HIFU is effective in treating renal, lung, and prostate cancer in males (Liu *et al*., 2024). In 2010, an Oxford team of researchers found that 7 out of 15 patients treated with HIFU had renal tumor ablation after 12 days of treatment, and after follow-up of 2 and half years, two two-thirds of the total patients had tumor ablation (Ritchie *et al*., 2010). Similarly, another in vivo study conducted on HIFU against swine pancreatic tumor confirmed the tumor ablation without damaging the nearby tissues and cells (Hwang *et al*., 2009). To treat prostate cancer a team of French researchers applied HIFU technique on 111 prostate cancer patients and found 95% tumor ablation with a patient survival rate of 89% (McCulloch *et al*., 2009; Rischmann *et al*., 2017). Another in vivo trial of HIFU (Sonablate) was conducted on 1032 patients diagnosed with medium and end-stage cancer. The treatment confirmed prostate tumor ablation of 81% patients with a survival rate of 97% after 5 years of treatment (Stabile *et al*., 2019). A more up-to-date study was conducted on 13 patients having colorectal liver metastasis. All patients were exposed to HIFU, which confirmed that these ultrasounds with high frequency and greater intensity can completely ablate the tumor of the liver (Yan *et al*., 2022; Yan *et al*., 2024).

Nowadays, a laparoscopic HIFU device has also been used to treat small kidney tumors. A researcher group from Oxford performed laparoscopic HIFU by a device known as Sonatherm, manufactured by an American company, on 22 patients from America and Vietnam and confirmed its effectiveness (Klingler *et al*., 2008). HIFU can be more effective when they are combined with some other conventional techniques such as magnetic resonance imaging ultrasound (MRI-US). The 20 patients with malignant prostate cancer have shown no suspicious lesion and complete removal of tumor by necrosis and acoustic cavitation (Yee *et al*., 2021). Another study was conducted on patients having prostate cancer to compare the effects of HIFU with histotripsy and confirmed that HIFU induced complete tumor ablation while histotripsy showed a partial response (Ashar *et al*., 2024). These findings suggest that HIFU alone or in combination with some modern techniques like IMRT and chemical drugs can be safe and reliable for tumor diagnosis and treatment while minimizing the side effects to the surrounding healthy tissues.

Besides its significance, one major challenge is that it is not very effective for deep tissue penetration and it reduces its effectiveness (Bates *et al*., 2021). While using HIFU, clinicians will also face problems because tumors can move during anatomical changes and during breathing (Sehmbi *et al*., 2021). So, the exact size and location of the tumor can influence the treatment efficacy. Lastly, they are expensive and specialized care centers in developed countries are not approachable for every patient.

Intensity modulated radiation therapy: IMRT is a specific beam technique of linear accelerated radiation therapy to ensure and deliver the radiation dose accurately at the three-dimensional structured tumor (Afrin and Ahmad, 2022). The major significance of this procedure lies in the fact that in IMRT, first is to decide the low dose to avoid normal and healthy tissues and then the dose rate is increased to target the malignant tumors (Yao and Chuan, 2024). IMRT is different from the conventional techniques because it uses determined doses, and a rotating linear accelerator is used to distribute variable doses of different intensities in each affected segment of the tumor (Da Silva Mendes *et al*., 2021).

During the conventional radiotherapy treatment of head and neck tumors, normally it happens that the functions of salivary glands are diminished, but IMRT dose distribution only destroys tumor cells without affecting functions of parotid, submaxillary, and sublingual glands (Nguyen *et al*., 2021). In one of the research studies held at Washington University, the IMRT technique was applied to 126 patients having head and neck tumors and confirmed the control rate up to 85% after two years of follow-up with normal functions of salivary glands (Chao *et al.*, 2003). A similar study on IMRT against head and neck tumors was conducted at Michigan University, USA. A total of 58 patients having head and neck tumors were treated with the IMRT technique and confirmed the control rate of 79% after two years of treatment by sparing the normal functions of parotid glands (Dawson *et al*., 2000). Another study conducted on 20 patients with primary head and neck tumor confirmed that 19 patients showed complete response to IMRT without disturbing the normal functions of parotid glands (Kuppersmith *et al*., 1999). Furthermore, IMRT has also been applied to 58 patients having nasopharyngeal carcinoma and confirmed the control rate of 98% after 31 months of follow-up (Lee *et al*., 2002). A recent update with 118 patients continues to demonstrate excellent locoregional control rates (Bucci *et al*., 2004). Rehman *et al*. (2022) conducted a study on 17 patients to confirm the effectiveness of IMRT against prostate cancer and concluded that 7-beam plans of IMRT are much effective than the 5-beam plan of conventional therapy in reducing prostate tumors without affecting the functions of seminal vesicles. Similarly, another study was conducted to compare the effects of IMRT with conventional radiographic techniques against prostate cancers. The study showed that IMRT treated patients showed less acute and late urinary toxicities with less risk of rectal bleeding (2%) as compared to three-dimensional conformal radiation therapy (3D-CRT), who have shown rectal bleeding up to 10% after two years of treatment (Zelefsky *et al*., 2000). A comparative study of IMRT with 3-D CRT was conducted on different patients who have prostate cancer. Different dose rates were prescribed and adjusted for both the treatments and the data confirmed the control rate up to 95% for those patients treated with IMRT (Kirichenko *et al*., 2006). This study also confirmed the significance and safety of the IMRT technique and its better use in the future against all types of malignant tumors with fewer side effects to normal tissues.

No doubt, it is very significant, but it requires very long treatment time because it requires more radiation beams to be distributed in a precise and controlled manner. It is very difficult for disabled or younger patients to still for a longer period of time. Furthermore, high cost, skillful planning, and deficiency of specialized persons can reduce its effectiveness (Verma *et al*., 2016). Additionally, IMRT is very beneficial for superficial and deep tumors, but it is not the best option for those tumors located in motion-prone areas, including the lungs and abdomen. For this, IMRT requires four-dimensional, advanced imaging and motion management (Mohan and Bortfeld, 2006). Finally, late side effects of IMRT as compared to conventional techniques are still a matter of concern and scientists are working on it for further modification (Wortel *et al*., 2016). Despite this, new innovations, development in technology, and advanced imaging are making it more convenient and effective technique in modern radiation oncology.

Image-guided radiation therapy: IGRT is a modern technology that uses imaging shapes to increase precision and accuracy at tumor-targeted areas (De Los Santos *et al*., 2013). This technique is involved in real-time images (CT scan, MRI, and ultrasounds) by tracking the tumor movement due to fluid accumulation, organs motion, muscle activity, breathing, patients' position, and vascular pulsation (Sharma *et al*., 2022). It also allows oncologists to adjust the volume of radiation according to tumor size and shape because tumors can shrink or grow during fluid accumulation or vascular pulsation. Once the size, shape, and position of the tumor are precisely determined, radiation can accurately target the tumor cells without damaging the nearby healthy tissues (De Crevoisier *et al*., 2022; García-Figueiras *et al*., 2024).

IGRT system consists of the image recording system, standard images for comparison with original tumor images, a comparison software, and a protocol of correction methodologies (Yamashita *et al*., 2024). This technique works by targeting the DNA of tumor cells by creating free radicals during radiation therapy (Srinivasan *et al*., 2024). These free radicals, in turn, damage the DNA strands either directly or indirectly, and the cells undergo apoptosis. Tumor cells are hypoxic due to improper angiogenesis and incomplete proliferations, which make them more resistant to radiation, but due to precise positions and accurate doses, the radiations properly target the tumor cells and cause damage (Koka *et al*., 2022). The online and offline correction strategies may also be adopted to effectively reduce systemic and random errors (Abubakar *et al*., 2021). The estimated set-up error for all the regions should not be more than 5mm. If it is greater than 5mm, then there is a dire need for readjustment to take better and accurate images; otherwise, it can damage the healthy surrounding tissues (Abubakar *et al*., 2021).

IGRT has been applied on various anatomical districts, including the breast, brain, head and neck, prostate, cervix, kidneys, lungs, and paraspinals in both animals and humans (Mireștean *et al*., 2023). A study on 56 patients confirmed the significance of the IGRT technique, which reduced the error up to 19% and better control rate of head and neck tumors (Zumsteg *et al*., 2012). A comparative study on 94 patients diagnosed with cervical cancer was conducted to check the effectiveness of IGRT against conventional therapies. The serum tumor marker level and Karnofsky performance status (KPS) scores were also determined. The first group of 47 patients was treated with the IGRT technique, while the second group of another 47 patients was treated with 3D-CRT radiations, and the results confirmed that the IGRT-treated group showed 97.87% effectiveness while the effectiveness for the 3D-CRT group was 74.46%. The decreased serum tumor marker level and increased KPS score confirmed that IGRT enhances the survival rate of cervical cancer patients (You and Hou, 2022). Another group of researchers also confirmed the precision, accuracy, and effectiveness of the IGRT technique in prostate cancer patients with low incidence of side effects (Franzone *et al*., 2016; Ríos *et al*., 2018). Clinical practices have demonstrated that IGRT satisfies the fundamental requirements of precision and accurate therapy by providing increased quantity of dosage at the targeted area with minimum dose to the nearby healthy tissues, supported by imaging equipment for real time monitoring of malignancies and normal cells (Gadducci and Cosio, 2020).

One primary limitation is the need for more images, which makes the treatment session longer. Besides the significance of imaging, it can delay the treatment time and make it less convenient for elder and disabled patients (De Los Santos *et al*., 2013). Similar to IMRT, IGRT also faces the same problem when addressing the treatment of tumors present in the diaphragm, lungs, and abdomen (Vergalasova *et al*., 2017). Furthermore, the cost-effectiveness of the IGRT system makes it less valuable, and it is not within the reach of every clinician and common people (Baumann *et al*., 2008). Lastly, IGRT is still uncertain regarding long-term outcomes. Patients are facing side effects and recurrence of secondary tumors (Shen *et al*., 2022). Ongoing research and advanced technology such as real-time adaptive therapy are key components in overcoming these limitations and making it more approachable and attractive. Some of the important information related to modern non-invasive radiographic techniques is given in Table 2. The mechanism of these modern techniques is also elaborated in Fig. 3.

Future directions: All the modern therapies mentioned above are very effective in the treatment of malignant tumors but have certain limitations as well. In the future these therapies can be more effective, personalized, and accessible if they are combined with new technologies. For example, the use of biomarkers will enable clinicians to identify malignant tumors more precisely and will lead to tailored treatment. Similarly, the synergistic potential of PBT with immunotherapy and nanomedicine will also be an exciting avenue. Proteomic and genomic profiling for molecular and genetic structures of tumor cells and tissues will make CIRT therapy more effective and personalized. Technologists are operative in making accelerator designs (ion accelerators) to reduce their size and make them cost-effective to ensure their availability. Researchers are also working on an adaptive HIFU system for the adjustment of controlled radiation delivery to tumor tissue that will increase its effectiveness and safety to both the clinicians and patients. Additionally, the combination of HIFU with immunotherapy will release tumor antigens and boost the anti-tumor immune response. It can be used for the treatment of neurological disorders such as Parkinson's disease, epilepsy, and Alzheimer's disease. Furthermore, the modernized adaptive radiotherapy is going to combine with IMRT protocols. This will make more accurate treatment plans based on tumor volume, either it is expanding or shrinking during breathing or due to patient's posture. At the present time, researchers are working on radio genomics and investigating the genetic and molecular structure of the tumors. This will help them to guide dose escalation and make careful decisions. The combination of genetic markers in the near future will also enhance IMRT treatment accuracy by minimizing the side effects. Similarly, in adaptive IGRT, scientists are focusing on the use of functional images like diffusion-weighted MRI and contrast imaging. This will enable researchers and clinicians to better differentiate tumor tissues and they will plan the treatment protocols and will optimize the dose delivery. Finally, all these techniques will be more functional when they are combined and done through artificial intelligence and machine learning procedures.

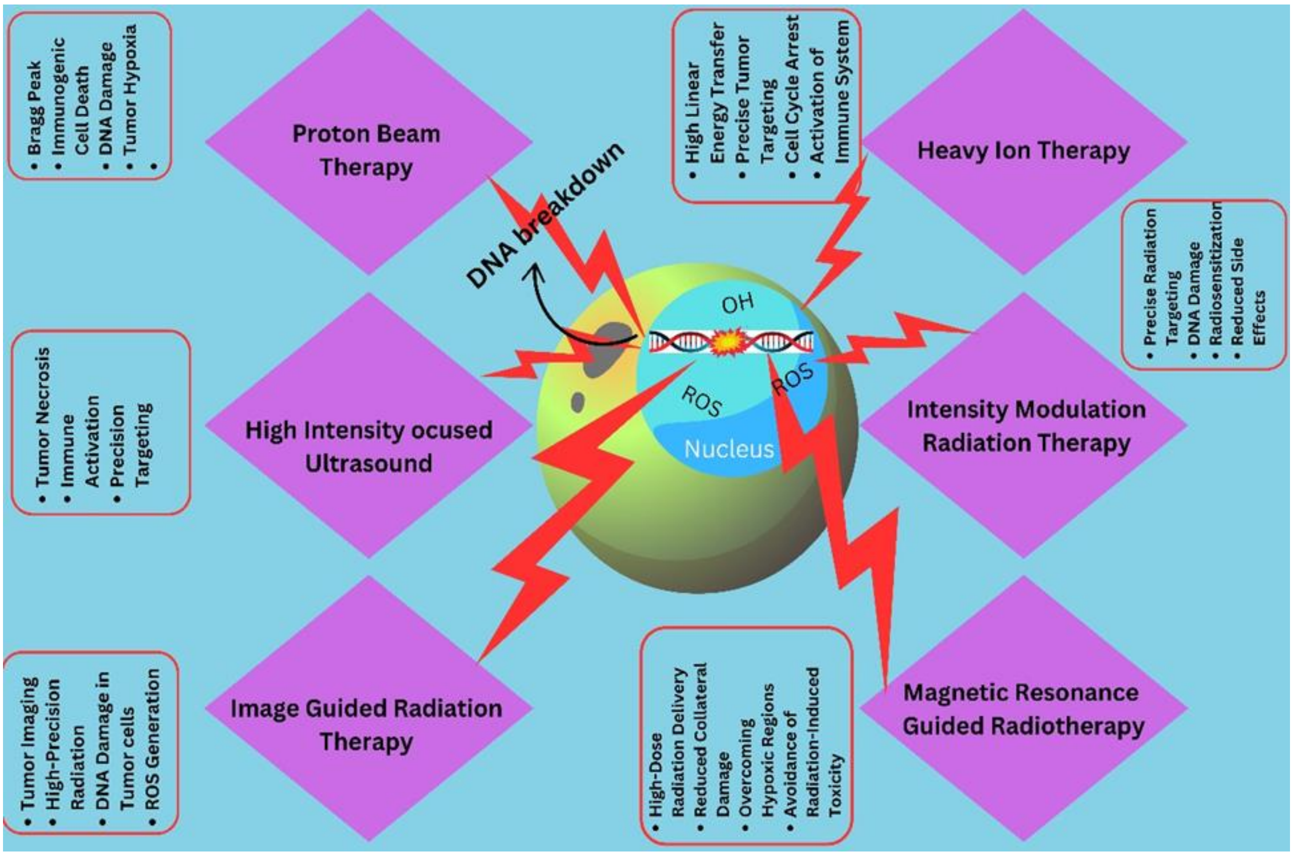

Fig. 3: Mechanism of action of non-invasive radiographic techniques against malignant tumors.

Table 2: Non-invasive modern radiographic techniques for the treatment of malignant tumors and their possible outcomes and limitations

Technique name	Types	Method	Dose rate	Application in malignant tumors	Tumor of a specific organ	Species	Possible outcome	Limitations	References
Proton beam therapy	Particle therapy	A-particle radiation	60-250MeV	Deep tissue tumors	Brain and spinal cord	Humans	minimal damage to normal tissues	High cost	Araya *et al.*, 2023
Heavy ion therapy	Particle therapy	Carbon/iron ions	2-4 Gy	Radio-resistant tumors	Brain, liver, lungs, and bones	Humans	High precision and minimal damage to normal cells	Requires specialized facilities	(Mairani 2024)
Magnetic resonance guided focused ultrasound	Image guided therapy	MRI and ultrasound	Variable	Peripheral tissues	Brain and bone	Humans	Precise targeting with minimal damage	Requires MRI compatibility	(Meng *et al.*, 2024)
High intensity focused ultrasound	Thermal ablation	Ultrasound waves	Variable	Solid tumor ablation	Prostate and liver	Humans	Tumor shrinkage	Limited penetration	(Peretsman *et al.*, 2024)
Intensity modulated radiation therapy	External beam radiation	System controlled radiations	1.8-2.2 Gy	Solid tumor treatment	Brain, head, neck, and lungs	Humans and canines	Targeted destruction	Advanced planning and expertise	(Budrukkar *et al.*, 2024)
Image guided radiation therapy	External beam radiation	Real-time images for accuracy and precision	1.8-2.2 Gy	Treatment with positioning and motioning	Brain, lungs, prostate, head and neck	Humans	Enhanced accuracy and minimal destruction to normal tissues	Require advanced imaging	Boldrini *et al.*, 2024
Electroporation based therapy	Non-thermal	Electric shocks	-	Deep tissue tumors	Liver and spleen	Humans and canines	Enhanced accuracy	Requires anesthesia	(Salameh *et al.*, 2024)
Cyberknife radiosurgery	Robotic type	Image-guided radiations	-	Deep organ tumors	Liver and spleen	Humans	High precision	Not used for large tumors	Javadnia *et al.*, 2025
Gamma knife radiosurgery	Stereotactic radiotherapy	Focused radiations	Variable	Deep and peripheral tumors	Brain	humans	High precision	Requires multiple sessions	(Spina *et al.*, 2024)

Conclusions: Non-invasive radiographic techniques are very helpful in the early detection, diagnosis and treatment of malignant tumors in humans and animals. The conventional techniques, such as X-rays, cryotherapy, cauterization, and laser beam ablation, are effective for the treatment of malignant tumors but have certain limitations. The modern techniques, including PTB, Heavy Ion therapy, HIFU, IMRT, and IGRT, provide detailed anatomical and physiological insights without any surgical intervention. These techniques are invaluable tools for clinicians to detect tumors more precisely and accurately. These techniques are very complex and cost-effective, but with the advancement of new technology, they will be available to every corner of the globe.

REFERENCES

Abubakar A, Zamri NAM, Shaukat SI, *et al.*, 2021. Automated algorithm for calculation of setup corrections and planning target volume margins for offline image-guided radiotherapy protocols. J. Appl Clin Med Phys 22:137-146.

Afrin KT and Ahmad S, 2022. Is IMRT or VMAT superior or inferior to 3D conformal therapy in the treatment of lung cancer? A brief literature review. J Radiother Pract 21:416-420.

Ahmad MY, Liu S, Tegafaw T, *et al.*, 2023. Heavy metal-based nanoparticles as high-performance x-ray computed tomography contrast agents. Pharm 16:1463.

Albano D, Benenati M, Bruno A, *et al.*, 2021. Imaging side effects and complications of chemotherapy and radiation therapy: a pictorial review from head to toe. Insights Imaging 12:76.

Ali Z, Hamdoun A and Alattaya A, 2024. Advances in radiological techniques for cancer diagnosis: a narrative review of current technologies. Health Nexus 2:43-56.

Alterio D, Vincini MG, Volpe S, *et al.*, 2024. A multicenter high-quality data registry for advanced proton therapy approaches: the POWER registry. BMC cancer 24:333.

Ambrose S, Khan AMA, Liaqat I, *et al.*, 2025. Targeted and efficient therapeutic effect of nanoparticles against malignant tumor: Nanoparticles against tumor. Lett Anim Biol 5:19-29.

Amin SA, Khatun S, Gayen S, *et al.*, 2023. Are inhibitors of histone deacetylase 8 (HDAC8) effective in hematological cancers especially acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)? Eur J Med Chem 258: 115594.

Andreucci M, Solomon R and Tasanarong A, 2014. Side effects of radiographic contrast media: pathogenesis, risk factors, and prevention. BioMed Res Int 2014:741018.

Araya M, Ishikawa H, Nishioka K, *et al.*, 2023. Proton beam therapy for muscle-invasive bladder cancer: A systematic review and analysis with Proton-Net, a multicenter prospective patient registry database. J Rad Res 64(1):i49-i58.

Asadian S, Mirzaei H, Kalantari BA, *et al.*, 2020. β-radiating radionuclides in cancer treatment, novel insight into promising approach. Pharmacol Res 160:105070.

Ashar H and Ranjan A, 2023. Immunomodulation and targeted drug delivery with high intensity focused ultrasound (HIFU): Principles and mechanisms. Pharmacol Ther 244:108393.

Ashar H, Singh A, Kishore D, *et al.*, 2024. Enabling chemo-immunotherapy with HIFU in canine cancer patients. Ann Biomed Eng 52:1859-1872.

Bahrami H and Tafrihi M, 2023. Global trends of cancer: The role of diet, lifestyle, and environmental factors. Cancer Innov 2:290-301.

Bates AS, Ayers J, Kostakopoulos N, *et al.*, 2021. A systematic review of focal ablative therapy for clinically localised prostate cancer in comparison with standard management options: limitations of the available evidence and recommendations for clinical practice and further research. Eur Urol Oncol 4:405-423.

Baumann M, Hölscher T, and Zips D, 2008. The future of IGRT–cost benefit analysis. Acta Oncol 47:1188-1192.

Baust JG, Gage AA, Johansen TEB, *et al.*, 2014. Mechanisms of cryoablation: clinical consequences on malignant tumors. Cryobiology 68:1-11.

Beniwal N, Verma A, Putta CL, *et al.*, 2024. Recent trends in bio-nanomaterials and non-invasive combinatorial approaches of photothermal therapy against cancer. Nanotheranostics 8:219.

Berben L, Floris G, Wildiers H, Hatse S, 2021. Cancer and aging: two tightly interconnected biological processes. Cancers 13:1400.

Boice JD, Cohen SS, Mumma MT, *et al.*, 2024. Mortality among medical radiation workers in the United States, 1965–2016, In: The Million Person Study of Low-Dose Radiation Health Effects. CRC Press, pp. 255-279.

Boire A, Burke K, Cox TR, *et al.*, 2024. Why do patients with cancer die? Nat Rev Cancer 24:578-589.

Boldrini L, D'Aviero A, De Felice F, *et al.*, 2024. Artificial intelligence applied to image-guided radiation therapy (IGRT): a systematic review by the Young Group of the Italian Association of Radiotherapy and Clinical Oncology (yAIRO). Radiol Med 129:133-151.

Borja NA, Silva-Smith R, Calfa C, *et al.*, 2024. Triple primary cancers: an analysis of genetic and environmental factors. CAPR 17:209-215.

Bortty JC, Bhowmik PK, Reza SA, *et al*., 2024. Optimizing lung cancer risk prediction with advanced machine learning algorithms and techniques. J Med Health Stud 5:35-48.

Bourgeois A, Horrill T, Mollison A, *et al*., 2024. Barriers to cancer treatment for people experiencing socioeconomic disadvantage in high-income countries: a scoping review. BMC Health Serv Res 24:670.

Braga J, 2015. Non-invasive imaging techniques. In: A Companion to Dental Anthropology. Wiley Online Library, pp:514-527.

Brook I, 2021. Early side effects of radiation treatment for head and neck cancer. Cancer/radiotherapie 25:507-513.

Bucci M, Xia P, Lee N, *et al*., 2004. Intensity modulated radiation therapy for carcinoma of the nasopharynx: an update of the UCSF experience. Int J Radiat Oncol Biol Phys 60:317-318.

Buckley D, 2012. Cryosurgery for nonmelanoma skin cancer, In: Modern Cryosurgery for Cancer. World Scientific, pp. 865-892.

Budrukkar A, Murthy V, Kashid S, *et al*., 2024. Intensity-modulated radiation therapy alone versus intensity-modulated radiation therapy and brachytherapy for early-stage oropharyngeal cancers: results from a randomized controlled trial. Int J Radiat Oncol Biol Phys 118:1541-1551.

Burnet NG, Mackay RI, Smith E, *et al*., 2020. Proton beam therapy: perspectives on the National Health Service England clinical service and research programme. Brit J Radiol 93:20190873.

Castello A, Olivari L and Lopci E, 2018. Adenoid cystic carcinoma: focus on heavy ion therapy and molecular imaging. Am J Nucl Med Mol Imaging 8:1-14.

Chao KSC, Ozyigit G, Tran BN, *et al*., 2003. Patterns of failure in patients receiving definitive and postoperative IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 55:312-321.

Chen C, Garlich J, Vincent K, *et al*., 2017. Postoperative complications with cryotherapy in bone tumors. J Bone Oncol 7:13-17.

Chen X, Ding Y, Yi Y, *et al*., 2024. Review of animal models of colorectal cancer in different carcinogenesis pathways. Dig Dis Sci 69:1583-1592.

Choi JH and Ro JY, 2021. The 2020 WHO classification of tumors of soft tissue: selected changes and new entities. Adv Anat Pathol 28:44-58.

Choi YM, Lee J, Kwak MK, *et al*., 2022. Recent changes in the incidence of thyroid cancer in Korea between 2005 and 2018: analysis of Korean National Data. Endocrinol Metab 37:791-799.

Ciambella CC and Takabe K, 2024. Cryotherapy in the treatment of early-stage breast cancer. World J Oncol 15:737-743.

Clemmons EA, Alfson KJ, and Dutton IJW, 2021. Transboundary animal diseases, an overview of 17 diseases with potential for global spread and serious consequences. Animals 11:2039.

Cozzi S, Augugliaro M, Ciammella P, *et al*., 2022. The role of interstitial brachytherapy for breast cancer treatment: an overview of indications, applications, and technical notes. Cancers 14:2564.

Crombé A, Simonetti M, Longhi A, *et al*., 2024. Imaging of Osteosarcoma: Presenting Findings, Metastatic Patterns, and Features Related to Prognosis. J Clinic Med 13:5710.

Cui Y, Yin S, Qin X, *et al*., 2022. Advances in the treatment of intraocular malignancies: A literature review. Front Med 9:975565.

Da Silva Mendes V, Nierer L, Li M, *et al*., 2021. Dosimetric comparison of MR-linac-based IMRT and conventional VMAT treatment plans for prostate cancer. Radiat Oncol 16:133.

Dawson LA, Anzai Y, Marsh L, *et al*., 2000. Patterns of local-regional recurrence following parotid-sparing conformal and segmental intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 46:1117-1126.

De Crevoisier R, Lafond C, Mervoyer A, *et al*., 2022. Image-guided radiotherapy. Cancer Radiother 26:34-49.

De Los Santos J, Popple R, Agazaryan N, *et al*., 2013. Image guided radiation therapy (IGRT) technologies for radiation therapy localization and delivery. Int J Radiat Oncol Biol Phys 87:33-45.

Demizu Y, Imai R, Kiyohara H, *et al*., 2021. Carbon ion radiotherapy for sacral chordoma: a retrospective nationwide multicentre study in Japan. Radiother Oncol 154:1-5.

Dowlatshahi K, Francescatti DS and Bloom KJ, 2002. Laser therapy for small breast cancers. The Am J Surg 184:359-363.

Durante M, Debus J and Loeffler JS, 2021. Physics and biomedical challenges of cancer therapy with accelerated heavy ions. Nat Rev Phys 3:777-790.

Ebadi M, Pankuch M, Boyer S, *et al*., 2024. Proton pencil beam scanning facilitates the safe treatment of extended radiation targets for hodgkin lymphoma: A Report from the Proton Collaborative Group Registry. Cancers 16:2736.

Efird JT, Davies SW, O'Neal WT *et al*., 2014. Animal viruses, bacteria, and cancer: a brief commentary. Front Public Health 2:14.

Eissa MM, Salem AE and El Skhawy N, 2024. Parasites revive hope for cancer therapy. Eur J Med Res 29:489.

Ellens NPK and Hynynen K, 2023. High-intensity focused ultrasound for medical therapy, In:Power Ultrasonics. Elsevier, pp. 577-598.

Fairweather D, Taylor RM and Simões R, 2024. Choosing the right questions–a systematic review of patient reported outcome measures used in radiotherapy and proton beam therapy. Radiother Oncol 191:110071.

Franzone P, Fiorentino A, Barra S, *et al*., 2016. Image-guided radiation therapy (IGRT): practical recommendations of Italian Association of Radiation Oncology (AIRO). Radiol Med 121:958-965.

Gadducci A and Cosio S, 2020. Neoadjuvant chemotherapy in locally advanced cervical cancer: review of the literature and perspectives of clinical research. Anticancer Res 40:4819-4828.

Gaikwad U, Bajpai J and Jalali R, 2024. Combinatorial approach of immuno-proton therapy in cancer: rationale and potential impact. Asia-Pac J Clini Oncol 20:188-197.

Galbraith K and Snuderl M, 2024. Molecular pathology of gliomas. Clin Lab Med 44:149-159.

Gao TY, Tao YT, Li HY, *et al*., 2024a. Cancer burden and risk in the Chinese population aged 55 years and above: A systematic analysis and comparison with the USA and Western Europe. J Glob Health 14:04014.

Gao Y, Chang CW, Mandava S, *et al*., 2024b. MRI-only based material mass density and relative stopping power estimation via deep learning for proton therapy: a preliminary study. Sci Rep 14:11166.

García-Figueiras R, Baleato-González S, Luna A, *et al*., 2024. How imaging advances are defining the future of precision radiation therapy. RadioGraphics 44:230152.

Gerstberger S, Jiang Q and Ganesh K, 2023. Metastasis. Cell 186:1564-1579.

Giannandrea and Fargnoli, 2017. Environmental factors affecting growth and occurrence of testicular cancer in childhood: an overview of the current epidemiological evidence. Children 4:1.

Goswami S, Adhikary S, Bhattacharya S, *et al*., 2024. The alarming link between environmental microplastics and health hazards with special emphasis on cancer. Life Sci 335:122937.

Gromek P, Senkowska Z, Płuciennik E, *et al*., 2024. Revisiting the standards of cancer detection and therapy alongside their comparison to modern methods. World J Methodol 14:92982.

Ha L, Tran A, Bui L, *et al*., 2023. Proportion and number of cancer cases and deaths attributable to behavioral risk factors in Vietnam. Int J Cancer 153:524-538.

Habash RWY, Bansal R, Krewski D, *et al*., 2007. Thermal therapy, Part III: ablation techniques. Crit Rev Biomed Eng 35:37-121.

Hall EJ and Brenner DJ, 2008. Cancer risks from diagnostic radiology. The Brit J Radiol 81:362-378.

Hamad MK, 2021. Bragg-curve simulation of carbon-ion beams for particle-therapy applications: A study with the GEANT4 toolkit. Nucl Eng Technol 53:2767-2773.

Hamada N, Hara T, Omura-Minamisawa M, *et al*., 2008. Energetic heavy ions overcome tumor radioresistance caused by overexpression of Bcl-2. Radiother Oncol 89:231-236.

Han J, Lee SH, Choi CY *et al*., 2022. Modified argon laser therapy for benign tumor of the eyelid. BMC Ophthalmol 22:383.

He S, Xia C, Li H, *et al*., 2024. Cancer profiles in China and comparisons with the USA: a comprehensive analysis in the incidence, mortality, survival, staging, and attribution to risk factors. Sci China Life Sci 67:122-131.

Helou J and Charas T, 2021. Acute and late side-effects after low dose-rate brachytherapy for prostate cancer; incidence, management and technical considerations. Brachytherapy 20:956-965.

Hou J, Wei R, Qian J, *et al*., 2019. The impact of the bone marrow microenvironment on multiple myeloma. Oncol Rep 42:1272-1282.

Hu J, Huang Q, Gao J, *et al*., 2021. Mixed photon and carbon-ion beam radiotherapy in the management of non-metastatic nasopharyngeal carcinoma. Front Oncol 11:653050.

Hu S, Zhang X, Melzer A, *et al*., 2023. Ultrasound-induced cavitation renders prostate cancer cells susceptible to hyperthermia: Analysis of potential cellular and molecular mechanisms. Front Genet 14:1122758.

Hudson EM, Slevin F, Biscombe K, *et al*., 2024. Hitting the target: developing high-quality evidence for proton beam therapy through randomised controlled trials. Clin Oncol 36:70-79.

Humm JL, Sartor O, Parker C, *et al*., 2015. Radium-223 in the treatment of osteoblastic metastases: a critical clinical review. Int J Radiat Oncol Biol Phys 91:898-906.

Hwang JH, Wang YN, Warren C, *et al*., 2009. Preclinical in vivo evaluation of an extracorporeal HIFU device for ablation of pancreatic tumors. Ultrasound Med Biol 35:967-975.

Ikawa H, Koto M, Fugo K, *et al*., 2024. Carbon-ion radiotherapy for clear cell odontogenic carcinomas. World J Surg Oncol 22:191.

Imam SS, 2021. The future of non-invasive ways to treat cancer. Int J Pharm Sci Res 12:4684-4696.

Islami F, Baeker Bispo J, Lee H, *et al*., 2024. American Cancer Society's report on the status of cancer disparities in the United States, 2023. CA Cancer J Clin 74:136-166.

Javadnia P, Bahadori AR, Ghanaatpisheh A, *et al*., 2025. The safety and efficacy of robotic radiosurgery and radiotherapy in the management of skull base tumors: a systematic review and meta-analysis. Neurosurg Rev 48:1-25.

Jiwei B, Abulimiti M, Yonglong J, *et al*., 2024. Proton beam therapy in a patient with secondary glioblastoma (32 years after postoperative irradiation of medulloblastoma): case report and literature review. Radiat Oncol 19:136.

Jones B, O'Grady E, Drage N, *et al*., 2023. The use of extra-oral bitewing radiographs for treatment planning in paediatric patients. Dental Update 50:767-770.

Kahan J, Martinez C and Tsien C, 2023. Critical appraisal of proton therapy for patients with Central Nervous System (CNS) Malignancies. Curr Treat Option Oncol 24:988-1003.

Karkos PD, Koskinas I, Stavrakas M, *et al*., 2021. Diode laser for laryngeal cancer:"980 nm" and beyond the classic CO2. Ear Nose Throat J 100:19-23.

Kasperski A and Heng HH, 2024. The spiral model of evolution: Stable life forms of organisms and unstable life forms of cancers. Int J of Mol Sci 25:9163.

Kirichenko AV, Ruth K, Horwitz EM, *et al*., 2006. Intensity modulated radiation therapy for prostate cancer: preliminary results on treatment morbidity compared to 3-D conformal radiation therapy. Int J Radiat Oncol Biol Phys 66:326.

Kitabayashi H, Shimada H, Yamada S, *et al*., 2006. Synergistic growth suppression induced in esophageal squamous cell carcinoma cells by combined treatment with docetaxel and heavy carbon-ion beam irradiation. Oncol Rep 15:913-918.

Klingler HC, Susani M, Seip R, *et al*., 2008. A novel approach to energy ablative therapy of small renal tumours: laparoscopic high-intensity focused ultrasound. Eur Urol 53:810-818.

Kobets T, Smith BPC and Williams GM, 2022. Food-borne chemical carcinogens and the evidence for human cancer risk. Foods 11:2828.

Koka K, Verma A, Dwarakanath BS, *et al*., 2022. Technological advancements in external beam radiation therapy (EBRT): An indispensable tool for cancer treatment. Cancer Manag Res 14:1421-1429.

Kumari S, Sharma N and Sahi SV, 2021. Advances in cancer therapeutics: Conventional thermal therapy to nanotechnology-based photothermal therapy. Pharmaceutics 13:1174.

Kuper H, Adami HO and Trichopoulos D, 2001. Infections as a major preventable cause of human cancer. J Int Med 249:61-74.

Kuppersmith RB, Greco SC, Teh BS, *et al*., 1999. Intensity-modulated radiotherapy: first results with this new technology on neoplasms of the head and neck. Ear Nose Throat J 78:238-251.

Laguna JC, García-Pardo M, Alessi J, *et al*., 2024. Geographic differences in lung cancer: focus on carcinogens, genetic predisposition, and molecular epidemiology. Therap Adv Med Oncol 16:17588359241231260.

Lara-Palomo IC, Capel-Alcaraz AM, García-López H, *et al*., 2024. Effects of monopolar pulsed-capacitive dielectric radiofrequency diathermy in patients with chronic low back pain: a randomised clinical trial. Sci Rep 14:14059.

Lee J, Shin NY, Lee SJ *et al*., 2024. Development of magnetic resonance-compatible head immobilization device and initial experience of magnetic resonance-guided radiation therapy for central nervous system tumors. Pract Radiat Oncol 14(5):e324-e333.

Lee N, Xia P, Quivey JM, *et al*., 2002. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. Int J Radiat Oncol Biol Phys 53:12-22.

Lewandowska A, Rudzki G, Lewandowski T, *et al*., 2022. Risk factors for the diagnosis of colorectal cancer. Cancer Control 29:10732748211056692.

Light E and Bridge P, 2024. Clinical indications for carbon-ion radiotherapy in the UK: A critical review. Radiography 30:425-430.

Lim YK and Kim D, 2021. Brachytherapy: A comprehensive review. Prog Med Phy 32:25-39.

Liu J, Feng YG, Zhang C, 2024. Advancements in high-intensity focused ultrasound for urological tumor research and application. Ann Med Surg 10:1097.

Logghe P, Verlinde R, Bouttens F, *et al*., 2016. Long term outcome and side effects in patients receiving low-dose I125 brachytherapy: a retrospective analysis. Int Braz J Urol 42:906-917.

Luo YH, Chiu CH, Kuo CHS, *et al*., 2021. Lung cancer in Republic of China. J Thorac Oncol 519-527.

Machado AFP, Perracini MR, Morais AdCSd, *et al*., 2017. Microwave diathermy and transcutaneous electrical nerve stimulation effects in primary dysmenorrhea: clinical trial protocol. Pain Management 7:359-366.

Makishima H, Yasuda S, Isozaki Y, *et al*., 2019. Single fraction carbon ion radiotherapy for colorectal cancer liver metastasis: a dose escalation study. Cancer Sci 110:303-309.

Mamun TI, Younus S and Rahman MH, 2024. Gastric cancer-epidemiology, modifiable and non-modifiable risk factors, challenges and opportunities: an updated review. *Cancer Treat Res Commun* 41:100845.

Mairani A. 2024. Innovative approaches to enhance high-LETd tumor targeting in carbon ion radiotherapy. J Health Technol 14:889-894.

Marchal C, Bey P, Hoffstetter S, *et al*., 2019. Ultrasound and microwave hyperthermia in the treatment of superficial human cancerous tumors, In: Hyperthermia in cancer treatment. CRC Press, pp.210-265.

Marino P, Mininni M, Deiana G, *et al*., 2024. Healthy lifestyle and cancer risk: modifiable risk factors to prevent cancer. Nutrients 16:800.

Matsumoto K, Imai R, Kamada T, *et al*., 2013. Impact of carbon ion radiotherapy for primary spinal sarcoma. Cancer 119:3496-3503.

Matsumoto Y, Fukumitsu N, Ishikawa H, 2021. A critical review of radiation therapy: from particle beam therapy (proton, carbon, and BNCT) to beyond. J Pers Med 11:825.

McCulloch P, Altman DG, Campbell WB, *et al*., 2009. No surgical innovation without evaluation: the Ideal recommendations. The Lancet 374:1105-1112.

Meng Y, Kalia LV, Kalia SK, *et al*., 2024. Current progress in magnetic resonance-guided focused ultrasound to facilitate drug delivery across the blood-brain barrier. Pharmaceutics 16:719.

Mireștean CC, Iancu RI and Iancu DPT, 2023. Image guided radiotherapy (igrt) and delta (δ) radiomics-an urgent alliance for the front line of the war against head and neck cancers. Diagnostics 13:2045.

Mohan R, 2022. A review of proton therapy–Current status and future directions. Prec Rad Oncol 6:164-176.

Mohan R and Bortfeld T, 2006. The potential and limitations of IMRT: a physicist's point of view, In: Image-Guided IMRT. Springer, pp. 11-18.

Mohan R, Grosshans D, 2017. Proton therapy–present and future. Adv Drug Deliv Rev 109:26-44.

Munson L, Moresco A, 2007. Comparative pathology of mammary gland cancers in domestic and wild animals. Breast Dis 28:7-21.

Nanayakkara AK, Boucher HW, Fowler JrVG, *et al*., 2021. Antibiotic resistance in the patient with cancer: Escalating challenges and paths forward. CA Cancer J Clin 71:488-504.

Newhauser WD and Zhang R, 2015. The physics of proton therapy. Phys Med Biol 60:155.

Nguyen ML, Cantrell JN, Ahmad S, *et al*., 2021. Intensity-modulated proton therapy (IMPT) versus intensity-modulated radiation therapy (IMRT) for the treatment of head and neck cancer: A dosimetric comparison. Medical Dosimetry 46:259-263.

Nitta H, Mizumoto M, Li Y, *et al*., 2024. An analysis of muscle growth after proton beam therapy for pediatric cancer. J Radiat Res 65:251-255.

Niitsu H, Mizumoto M, Li Y, *et al*., 2024. Tumor response on diagnostic imaging after proton beam therapy for hepatocellular carcinoma. Cancers 16:357.

Niu Z, Li Y, Chen W, *et al*., 2020. Study on clinical and biological characteristics of ameloblastic carcinoma. Orphanet J Rare Dis 15:1-9.

Nolen SC, Evans MA, Fischer A, *et al*., 2017. Cancer-incidence, prevalence and mortality in the oldest-old. A comprehensive review. Mech Ageing Dev 164:113-126.

Okada T, Kamada T, Tsuji H, *et al*., 2010. Carbon ion radiotherapy: clinical experiences at National Institute of Radiological Science (NIRS). J Radiat Res 51:355-364.

Oleson JR, 2019. The role of magnetic induction techniques for producing hyperthermia, In: Hyperthermia in Cancer Treatment. CRC Press, pp. 141-154.
Pace-Asciak P, Russell JO and Tufano RP, 2022. The treatment of thyroid cancer with radiofrequency ablation. Tech Vasc Interv Radiol 25:100825.
Padilla-Cabal F, Georg D and Fuchs H, 2018. A pencil beam algorithm for magnetic resonance image-guided proton therapy. Med Phys 45:2195-2204.
Paganetti H, Beltran C, Both S, *et al*., 2021a. Roadmap: proton therapy physics and biology. Phys Med Biol 66:05RM01.
Paganetti H, Botas P, Sharp GC, *et al*., 2021b. Adaptive proton therapy. Phys Med Biol 66:22TR01.
Pak H, Maghsoudi LH, Soltanian A, *et al*., 2020. Surgical complications in colorectal cancer patients. Ann Med Surg 55:13-18.
Parise M and Cristina S, 2009. High-order electromagnetic modeling of shortwave inductive diathermy effects. Prog Electromgn Res 92:235-253.
Parkin DM, Hämmerl L, Ferlay J, 2020. Cancer in Africa 2018: The role of infections. Int J Cancer 146:2089-2103.
Pereira FES, Jagatheesaperumal SK, Benjamin SR, 2024. Advancements in non-invasive microwave brain stimulation: A comprehensive survey. Phys Life Rev 48:132-161
Peretsman SJ, Emberton M, Fleshner N, *et al*., 2024. High-intensity focused ultrasound with visually directed power adjustment for focal treatment of localized prostate cancer: systematic review and meta-analysis. World J Urol 42:175.
Polańska A, Jenerowicz D, Paszyńska E, *et al*., 2021. High-Frequency ultrasonography—possibilities and perspectives of the use of 20 mhz in teledermatology. Front Med 8:619965.
Prasad RD, Sonawane KD, Prasad RS, *et al*., 2024. A review on livestock viral disease and their management. ES General 5:1227.
Protano C, Buomprisco G, Cammalleri V, *et al*., 2021. The carcinogenic effects of formaldehyde occupational exposure: a systematic review. Cancers 14:165.
Qiu H, Lou Y, Wang Z, *et al*., 2023. Factors influencing surgical choice and anxiety in patients with pulmonary nodules smaller than 8 mm. J Thorac Dis 15:6889.
Quadri SA, Waqas M, Khan I, *et al*., 2018. High-intensity focused ultrasound: past, present, and future in neurosurgery. Neurosurg Focus 44:E16.
Ragavendran C, 2024. Letter to Editor: Comment on, "Proton Beam radiation therapy for vestibular schwannomas–tumor control and hearing preservation rates: A systematic review and meta-analysis". Neurosurg Rev 47:1-1.
Rao K and Kumar S, 2014. The use of enucleation and chemical cauterization (Carnoy's) in the management of odontogenic keratocyst of the jaws. Indian J Otolaryngol Head Neck Surg 66:8-12.
Ray K and Stick M, 2015. Radiation and health effects, In: Handbook of Toxicology of Chemical Warfare Agents. Elsevier, pp.431-446.
Rehman A, Nasir MKR, Amjad N, et al., 2022. Dosimetric evaluation of treatment plans of 3DCRT & IMRT in prostate cancer EBRT. OALib Journal 9(12):1-14.
Ríos I, Vásquez I, Cuervo E, *et al*., 2018. Problems and solutions in IGRT for cervical cancer. Rep Pract Oncol Radiother 23:517-527.
Rischmann P, Gelet A, Riche B, *et al*., 2017. Focal high intensity focused ultrasound of unilateral localized prostate cancer: a prospective multicentric hemiablation study of 111 patients. Eur Urol 71:267-273.
Ritchie RW, Leslie T, Phillips R, *et al*., 2010. Extracorporeal high intensity focused ultrasound for renal tumours: a 3-year follow-up. BJU international 106:1004-1009.
Rucci L, Romagnoli P and Scala J, 2010. CO2 laser therapy in Tis and T1 glottic cancer: indications and results. Head Neck-J Sci Spec 32:392-398.
Salameh ZS, Aycock KN, Alinezhadbalalami N, *et al*., 2024. Harnessing the electrochemical effects of electroporation-based therapies to enhance anti-tumor immune responses. Ann Biomed Eng 52:48-56.
Sawicki T, Ruszkowska M, Danielewicz A, *et al*., 2021. A review of colorectal cancer in terms of epidemiology, risk factors, development, symptoms and diagnosis. Cancers 13:2025.
Schiller JT and Lowy DR, 2021. An introduction to virus infections and human cancer. Viruses and human cancer: from basic science to clinical prevention. Recent Results Cancer Res 217:1-11.
Sehmbi AS, Froghi S and de Andrade MO, *et al*., 2021. Systematic review of the role of high intensity focused ultrasound (HIFU) in treating malignant lesions of the hepatobiliary system. HPB 23:187-196.
Seneviratne D, Ishikawa H, Mao J, *et al*., 2022. Carbon ion radiotherapy in the management of non-small cell lung cancer. Precis Radiat Oncol 6:69-74.
Sharma M, Nano TF, Akkati M, *et al*., 2022. A systematic review and meta-analysis of liver tumor position variability during SBRT using various motion management and IGRT strategies. Radiother Oncol 166:195-202.
Shen Y, Chen JQ and Li XP, 2024. Differences between lung adenocarcinoma and lung squamous cell carcinoma: Driver genes, therapeutic targets, and clinical efficacy. Genes Dis 24:101374.
Shen Z, Qu A, Jiang P, *et al*., 2022. Re-irradiation for recurrent cervical cancer: a state-of-the-art review. Curr Oncol 29:5262-5277.
Shiba S, Okamoto M, Kiyohara H, *et al*., 2021. Impact of carbon ion radiotherapy on inoperable bone sarcoma. Cancers 13:1099.
Shibuya K, Katoh H, Koyama Y, *et al*., 2022. Efficacy and safety of 4 fractions of carbon-ion radiation therapy for hepatocellular carcinoma: a prospective study. Liver Cancer 11:61-74.
Shinozaki S, Kobayashi Y, Hayashi Y, *et al*., 2018. Efficacy and safety of cold versus hot snare polypectomy for resecting small colorectal polyps: Systematic review and meta-analysis. Dig Endoscop 30:592-599.
Skowronek J, 2017. Current status of brachytherapy in cancer treatment–short overview. J Contemp Brachytherapy 9:581-589.
Smith MR, Hussain M, Saad F, *et al*., 2022. Darolutamide and survival in metastatic, hormone-sensitive prostate cancer. N Eng J Med 386:1132-1142.
Soleymani T, Abrouk M and Kelly KM, 2017. An analysis of laser therapy for the treatment of nonmelanoma skin cancer. Dermatol Surg 43:615-624.
Spina A, Garbin E, Albano L, *et al*., 2024. Gamma Knife radiosurgery for central neurocytoma: a quantitative systematic review and meta-analysis. Neurosurg Rev 47:64.
Srinivasan D, Subbarayan R, Srivastava N, *et al*., 2024. A comprehensive overview of radiation therapy impacts of various cancer treatments and pivotal role in the immune system. Cell Biochem Funct 42:e4103.
Stabile A, Orczyk C, Hosking-Jervis F, *et al*., 2019. Medium-term oncological outcomes in a large cohort of men treated with either focal or hemi-ablation using high-intensity focused ultrasonography for primary localized prostate cancer. BJU international 124:431-440.
Stauffer PR and Goldberg SN, 2004. Introduction: thermal ablation therapy. Int J Hyperthermia 20:671-677.
Stone R, Carey E, Fader AN, *et al*., 2021. Enhanced recovery and surgical optimization protocol for minimally invasive gynecologic surgery: an AAGL white paper. J Minim Invasive Gynecol 28:179-203.
Sudo M, Tsutsui H and Fujimoto J, 2024. Carbon ion irradiation activates anti-cancer immunity. Int J Mol Sci 25:2830.
Talapko J, Talapko D, Katalinić D, *et al*., 2024. Health effects of ionizing radiation on the human body. Medicina 60:653.
Theodorescu D, 2004. Cancer cryotherapy: evolution and biology. Rev Urol 6:S9.
Tohme S, Simmons RL and Tsung A, 2017. Surgery for cancer: a trigger for metastases. Cancer Res 77:1548-1552.
Tubridy EA, Taunk NK and Ko EM, 2024. Treatment of node-positive endometrial cancer: chemotherapy, radiation, immunotherapy, and targeted therapy. Curr Treat Options Oncol 25:330-345.
Valdez-Salazar F, Jiménez-Del Rio LA, Padilla-Gutiérrez JR, *et al*., 2024. Advances in melanoma: from genetic insights to therapeutic innovations. Biomed 12:1851.
Vergalasova I, Li G, Kelsey CR, *et al*., 2017. Uncertainties of IGRT for lung cancer, In: Principles and Practice of Image-Guided Radiation Therapy of Lung Cancer. CRC Press, pp. 235-260.
Verma V, Mishra MV and Mehta MP, 2016. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. Cancer 122:1483-1501.
Vijayakumar S, Dhakshanamoorthy R, Baskaran A, *et al*., 2024. Drug resistance in human cancers-Mechanisms and implications. Life Sci 352:122907.
Virani SS, Ahmed KS, Jaraczewski T, *et al*., 2024. Cancer research funding in South Asia. J Cancer Policy 41:100489.
Warmuth M, Johansson T and Mad P, 2010. Systematic review of the efficacy and safety of high-intensity focussed ultrasound for the primary and salvage treatment of prostate cancer. Eur Urol 58:803-815.
Wills A and Obermair A, 2013. A review of complications associated with the surgical treatment of vulvar cancer. Gynecol oncol 131:467-479.
Wortel RC, Incrocci L, Pos FJ, *et al*., 2016. Late side effects after image guided intensity modulated radiation therapy compared to 3D-conformal radiation therapy for prostate cancer: results from 2 prospective cohorts. Int J Radiat Oncol Biol Phys 95:680-689.
Xu Z, Khokhlova TD, Cho CS, *et al*., 2024. Histotripsy: a method for mechanical tissue ablation with ultrasound. Ann Rev Biomed Eng 26:141-167.

Yamada S, Takiyama H, Isozaki Y, *et al*., 2021. Carbon-ion radiotherapy for colorectal cancer. J Anus Rectum Colon 5:113-120.

Yamashita K, Shimizu T, Miyabayashi K, *et al*., 2024. Utility of a skin marker–less setup procedure using surface-guided imaging: a comparison with the conventional laser-based setup in extremity irradiation. Radiol Phys Technol 17:569-577.

Yan L, Huang H, Lin J, *et al*., 2022. High-intensity focused ultrasound treatment for symptomatic uterine fibroids: a systematic review and meta-analysis. Int J hyperthermia 39:230-238.

Yan O, Wang S, Wang Q, *et al*., 2024. FLASH Radiotherapy: Mechanisms of biological effects and the therapeutic potential in cancer. Biomolecules 14:754.

Yao X and Chuan C, 2024. A review of validated techniques and tools for tumor intensity-modulated radiation therapy. Digit Med 10:e2400010.

Yao X, Li W, Fang D, *et al*., 2021. Emerging roles of energy metabolism in ferroptosis regulation of tumor cells. Adv Sci 8:2100997.

Yee CH, Chiu PKF, Teoh JYC, *et al*., 2021. High-Intensity Focused Ultrasound (HIFU) focal therapy for localized prostate cancer with MRI-US fusion platform. Adv Urol 2021:7157973.

Ying Y, Yahya N and Manan HA, 2024. Amide proton transfer MR imaging in the characterization of brain tumors: A review paper. J Radiat Res Appl Sci 17:101043.

Yoo SS, 2018. Technical review and perspectives of transcranial focused ultrasound brain stimulation for neurorehabilitation. Brain Neurorehabil 11:1-10

You X and Hou FY, 2022. Clinical efficacy of image-guided radiation therapy for cervical cancer and its impact on patients' serum tumor markers and Kps scores. J Oncol 2022:8536554.

Zelefsky MJ, Fuks Z, Happersett L, *et al*., 2000. Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. Radiother Oncol 55:241-249.

Zheng X, Liu Z, Bin Y, *et al*., 2024. Ionizing radiation induces vascular smooth muscle cell senescence through activating NF-κB/CTCF/p16 pathway. Biochim Biophys Acta Mol Basis Dis 1870:166994.

Zhu Z, Liu Y, Xu H, *et al*., 2023. Combined large cell neuroendocrine carcinoma, lung adenocarcinoma, and squamous cell carcinoma: a case report and review of the literature. J Cardiothorac Surg 18:254.

Zoubeidi A and Ghosh PM, 2021. Celebrating the 80th anniversary of hormone ablation for prostate cancer. Endocr Relate Cancer 28:1-10.

Zumsteg Z, DeMarco J, Lee SP, Steinberg ML, 2012. Image guidance during head-and-neck cancer radiation therapy: analysis of alignment trends with in-room cone-beam computed tomography scans. Int J Radiat Oncol Biol Phys 83:712-719.