



## 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

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#### 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.

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#### 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).

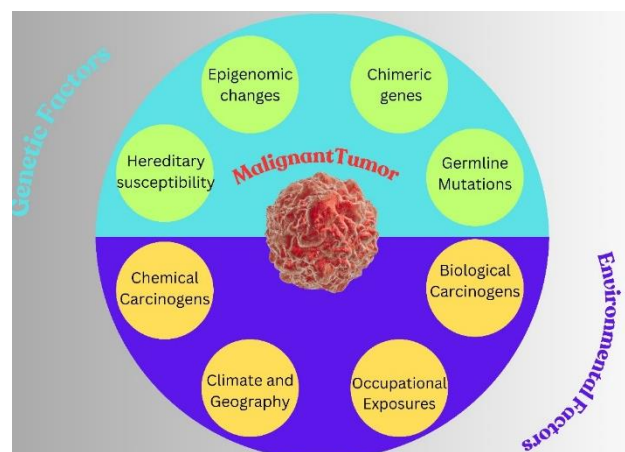
Cancer in animals causes significant economic losses in farm and companion animals (Efird *et al.*, 2014). For farm animals, it reduces the production of eggs, meat, milk, and hide (Bahrami and Tafrihi, 2023). While the cancer of reproductive organs leads to infertility and culling of the animals. Resources 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 more 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 towards 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 include 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 2.17 times higher risk, while obese has 1.27 times higher risk as compared to non-smokers and non-obese (Lewandowska *et al.*, 2022). In 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, 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  $\alpha$ ,  $\beta$ , and  $\gamma$  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.*, 2023). These techniques with their mode of actions are described below.

**Proton beam therapy:** Proton beam therapy (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 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).

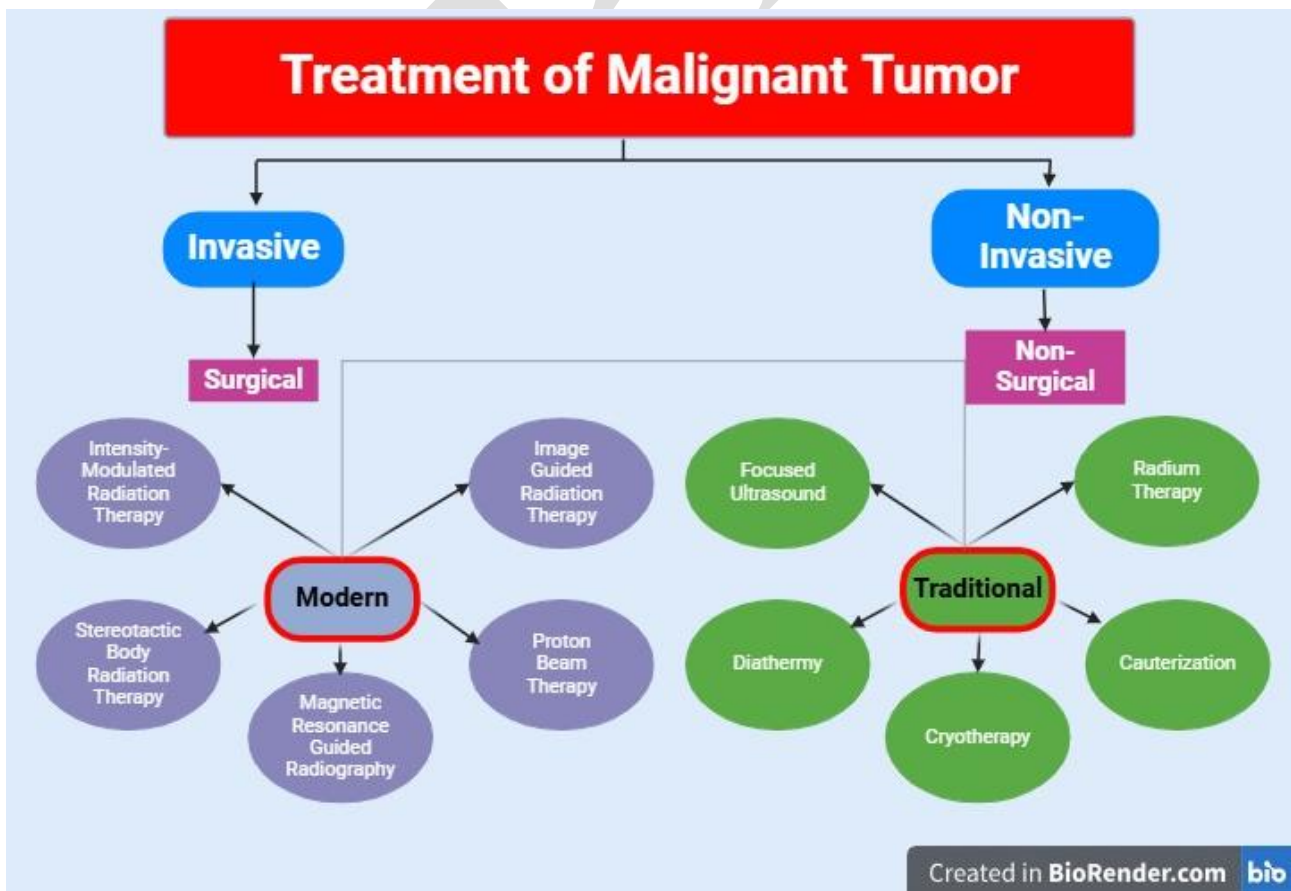


Fig. 2: Conventional and modern radiographic techniques used for the diagnosis and treatment of malignant tumors.

**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 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	Fear 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 and recurrence	(Parise Cristina, 2009; Oleson, 2019)
Laser therapy	CO <sub>2</sub> 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	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 other half group was exposed by conventional photon beams. Results have shown 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 a 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 and 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). 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 rate 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 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, enhanced maturation process (Zheng *et al.*, 2024). Carbon ions also have the ability to kill cells at cell cycle stages including 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 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 evidences for the production of secondary tumor cells have been observed but a series of experiment has been carried out on gland tumors of mouse 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/cm<sup>2</sup> respectively (Polańska *et al.*, 2021). While the 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 area and volume of tumor cells with intensities more than 1500 W/cm<sup>2</sup> and cause ablation of the targeted area (Yoo, 2018). HIFU cause tissue necrosis in generating high temperature of more than 80 °C which causes 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 less chances of tissue damage to nearby cells. On the other side HIFU causes 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 did not produce thermal effects (Xu *et al.*, 2024).

HIFU is effective to treat renal, lungs, 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 patients have renal tumor ablation after 12 days of treatment and after follow up of 2 and half years two third of the total patients have tumor ablation (Ritchie *et al.*, 2010). Similarly, another in vivo study conducted on HIFU against swine pancreatic tumor which 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 conducted on 13 patients having colorectal liver metastasis. All patients were exposed to HIFU that confirmed that these ultrasounds with high frequency and greater intensity can completely ablate the tumor of liver (Yan *et al.*, 2022).

Now a days 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 treated 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 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 treatments 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 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 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 cell without affecting functions of parotid, sub maxillary and sublingual glands (Nguyen *et al.*, 2021). In one of the research held at Washington university, the IMRT

technique was applied on 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 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 and 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 on 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 is 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 (Zelevsky *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 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 IMRT technique and its better use in future against all types of malignant tumors with less side effects to normal tissues.

No doubt it is very significant but it requires very long treatment time because it required more radiation beams to be distributed in a precise and controlled manner. It is very difficult for disabled or younger patients to still for 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 best option for those tumors located in motion-prone areas including 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 radiations according to tumor size and shapes because tumors can shrink or grow during fluid accumulation or vascular pulsation. Once the size, shape and position of tumor is 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 is worked by targeting the DNA of tumor cells by creating free radicals during radiation therapy (Srinivasan *et al.*, 2024). These free radicals in turn damaged 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 radiations but due to precise positions and accurate dose, 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 the 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 of 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 breast, brain, head and neck, prostate, cervix, kidneys, lungs, and paraspinals in both animals and humans (Mireştean *et al.*, 2023). A study on 56 patients confirmed the significance of 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 were treated with IGRT technique while the second group of another 47 patients was treated with 3D-CRT radiations and the results confirmed that IGRT treated group showed 97.87% effectiveness while the effectiveness for 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 IGRT technique in prostate cancer patients with low incidence of side effects (Franzone *et al.*, 2016; Ríos *et al.*, 2018). Clinical practices has 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 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, 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 it cost-effective to ensure its availability. Researchers are also working on 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 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. In 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 weighed 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

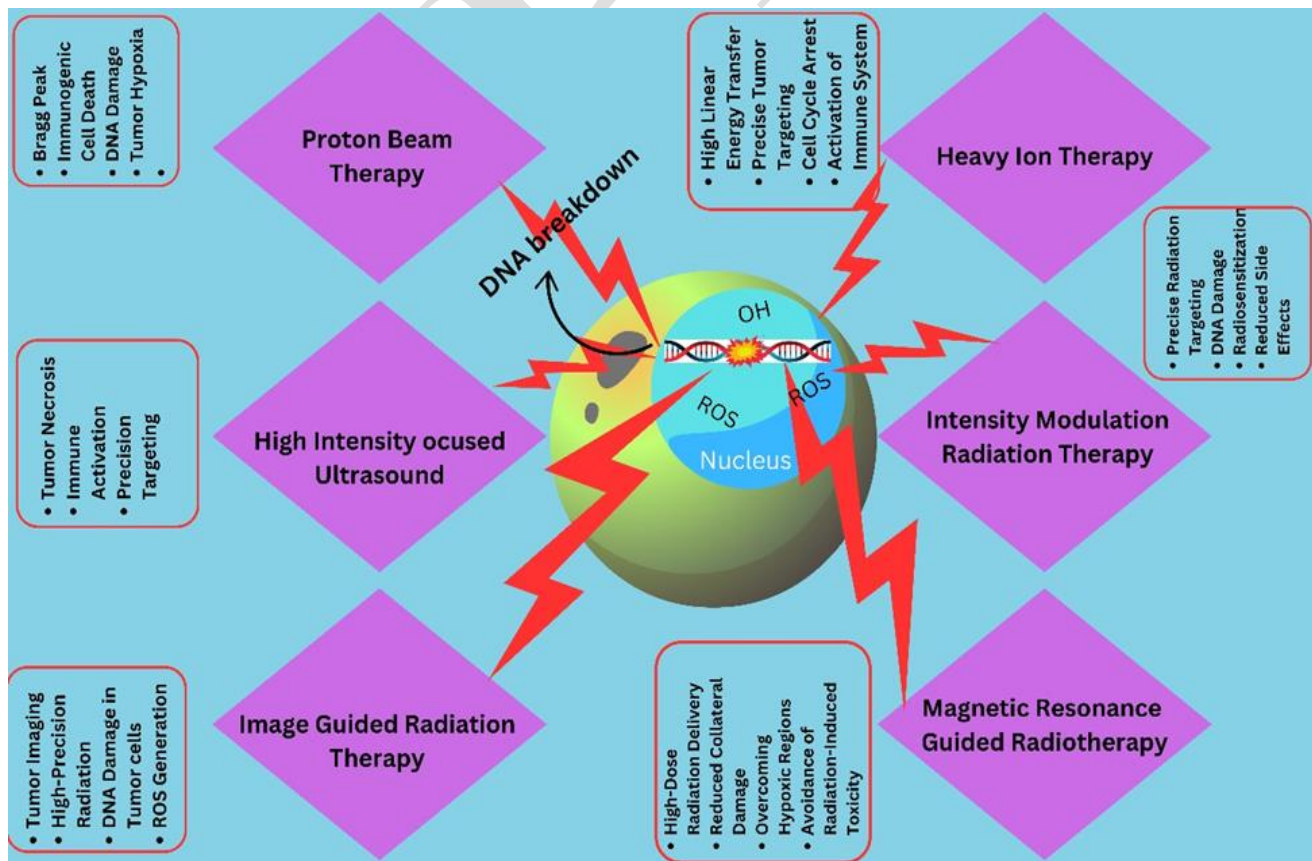


Fig. 3: Mechanism of action of non-invasive radiographic techniques against malignant tumors.

**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 <i>et al.</i> , 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 <i>et al.</i> , 2024)
High intensity focused ultrasound	Thermal ablation	Ultrasound waves	Variable	Solid tumor ablation	Prostate and liver	Humans	Tumor shrinkage	Limited penetration	(Peretsman <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 2024
Electroporation based therapy	Non-thermal	Electric shocks	-	Deep tissue tumors	Liver and spleen	Humans and canines	Enhanced accuracy	Requires anesthesia	(Salameh <i>et al.</i> , 2024)
Cyberknife radiosurgery	Robotic type radiations	Image-guided radiations	-	Deep organ tumors	Liver and spleen	Humans	High precision	Not used for large tumors	Javadnia <i>et al.</i> , 2025
Gamma knife radiosurgery	Stereotactic radiotherapy	Focused radiations	Variable	Deep and peripheral tumors	Brain	humans	High precision	Requires multiple sessions	(Spina <i>et al.</i> , 2024)

will be more functional when they are combined and done through artificial intelligence and machine learning procedures.

**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 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.

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