

The Evolution Of Radiology In Cancer Diagnosis And Management

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ABSTRACT

The evolution of radiology has significantly transformed the landscape of cancer diagnosis and management, playing a pivotal role in enhancing patient outcomes. From the groundbreaking discovery of X-rays by Wilhelm Conrad Röntgen in 1895 to the advent of advanced imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), radiology has continually adapted to meet the challenges of oncology. Early radiological techniques primarily focused on detecting skeletal metastases, but advancements in imaging technology have expanded capabilities to include detailed visualization of soft tissues, functional imaging, and real-time assessments of tumor metabolism. Today, modern imaging techniques are integral to the entire continuum of cancer care, facilitating early detection, accurate staging, treatment planning, and monitoring of therapeutic responses. The incorporation of artificial intelligence

(AI) and machine learning into radiology is further revolutionizing cancer diagnostics, allowing for enhanced image analysis, automated detection of tumors, and improved predictive modeling based on radiomic features. These advancements not only increase diagnostic accuracy but also streamline workflows, enabling radiologists to focus on complex clinical decision-making. Despite these advancements, challenges remain, including the need for standardization in imaging protocols, addressing algorithmic biases in AI applications, and ensuring the ethical use of patient data. As the field continues to evolve, the integration of radiology into personalized medicine holds great promise for tailoring treatment strategies to individual patients based on their unique tumor characteristics. In conclusion, the evolution of radiology in cancer diagnosis and management has been marked by significant technological advancements and innovative practices that enhance the quality of care. Continued research and collaboration among radiologists, oncologists, and data scientists will be essential to harness the full potential of radiology in combating cancer and improving patient outcomes in the future.

1. Introduction

Cancer remains one of the leading causes of morbidity and mortality globally, with an estimated 19.3 million new cases and nearly 10 million deaths recorded in 2020 (1). This staggering statistic underscores the urgent need for effective strategies in cancer prevention, diagnosis, and management. The complexity of cancer as a disease, characterized by its heterogeneous nature and the myriad of factors influencing its progression, necessitates a multifaceted approach to care. Early and accurate diagnosis is paramount for effective cancer management, as timely intervention can significantly improve patient outcomes and survival rates. Radiology has been at the forefront of this endeavor, providing critical insights that guide clinical decision-making.

The evolution of radiological techniques has dramatically transformed the landscape of oncology, influencing how cancer is diagnosed, staged, and treated. From the initial use of X-rays to the sophisticated imaging modalities available today, radiology has continually adapted to the changing needs of cancer care. Early radiological practices primarily focused on detecting skeletal metastases and assessing the extent of disease through basic imaging techniques. However, with advancements in technology, the field has expanded to include a variety of imaging modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), each offering unique advantages in terms of resolution, sensitivity, and specificity.

This review will explore the historical development of radiology, tracing its origins and significant milestones that have shaped its current practice. We will delve into the current state of imaging modalities, highlighting their roles in cancer diagnosis and management, as well as their contributions to treatment planning and monitoring.

Additionally, we will examine the integration of advanced technologies such as artificial intelligence (AI) and machine learning into radiology, which have the potential to enhance diagnostic accuracy and improve workflow efficiency. These technologies are revolutionizing the way radiologists interpret images and make clinical decisions, paving the way for a future where personalized medicine can be more effectively implemented.

Furthermore, we will address the challenges and opportunities that lie ahead for the field of radiology in oncology. As the demand for imaging services continues to grow, it is crucial to consider the implications of increased data volume, the need for standardization in imaging protocols, and the ethical considerations surrounding the use of AI in clinical practice. By understanding the historical context, current advancements, and future directions of radiology in cancer diagnosis and management, we can better appreciate its essential role in improving patient outcomes and shaping the future of cancer care. Through this comprehensive exploration, we aim to highlight the critical importance of radiology in the fight against cancer and the ongoing innovations that promise to enhance its effectiveness in the years to come.

2. Historical Development of Radiology

2.1 The Birth of Radiology

The field of radiology began with the discovery of X-rays by Wilhelm Conrad Röntgen in 1895. Röntgen's groundbreaking work allowed for the visualization of internal structures, paving the way for the use of X-rays in medical diagnosis. Initially, radiography was primarily utilized for examining skeletal injuries and detecting foreign bodies (2). The first clinical application of X-rays in cancer diagnosis emerged in the early 20th century, particularly for detecting bone metastases (3).

2.2 Advancements in Imaging Technology

The mid-20th century saw significant advancements in imaging technology. The introduction of fluoroscopy allowed for real-time imaging, enhancing the diagnostic capabilities of radiologists (4). The development of computed tomography (CT) in the 1970s revolutionized the field by providing cross-sectional images of the body, enabling more accurate tumor localization and staging (5). Magnetic resonance imaging (MRI), introduced in the 1980s, offered superior soft tissue contrast, making it particularly valuable for brain and spinal tumors (6).

2.3 The Rise of Nuclear Medicine

Nuclear medicine emerged as a distinct specialty in the 1950s, utilizing radioactive isotopes for diagnostic and therapeutic purposes. Positron emission tomography (PET), developed in the 1970s, allowed for functional imaging of tumors, providing insights into metabolic activity and aiding in cancer diagnosis and treatment response assessment (7).

3. Modern Imaging Modalities in Cancer Diagnosis and Management

The landscape of cancer diagnosis and management has been profoundly shaped by the development of modern imaging modalities. These technologies not only enhance our ability to detect and characterize tumors but also play a crucial role in guiding treatment decisions and monitoring patient progress. This section will delve into the various imaging modalities currently employed in oncology, including X-ray and fluoroscopy, computed tomography (CT), and magnetic resonance imaging (MRI), highlighting their individual contributions and significance in cancer care (8).

3.1 X-ray and Fluoroscopy

Despite the advent of advanced imaging technologies, conventional X-ray and fluoroscopy remain essential tools in cancer diagnosis. X-rays have been a staple in medical imaging since their discovery, and they continue to be widely used for initial evaluations of suspected malignancies. Their ability to provide quick and accessible imaging makes them particularly valuable in emergency settings and for screening purposes. X-rays are commonly employed to assess the chest for lung cancers, detect bone metastases, and evaluate abnormalities in the skeletal system. The simplicity and speed of X-ray imaging allow for rapid diagnosis, which is critical in acute care situations. Fluoroscopy, a technique that utilizes X-rays to create real-time moving images, is employed for guiding procedures such as biopsies and catheter placements. This dynamic imaging modality is particularly beneficial in interventional radiology, where accurate placement of instruments is essential for the success of minimally invasive procedures (9). Fluoroscopy allows physicians to visualize anatomical structures and monitor the progress of interventions in real time, reducing the risk of complications and improving patient safety. Furthermore, fluoroscopy can be used to assess gastrointestinal cancers by evaluating the motility and function of the digestive tract, aiding in the diagnosis of conditions such as esophageal and colorectal cancers.

While newer imaging modalities have emerged, the role of X-ray and fluoroscopy in cancer diagnosis and management remains vital. Their accessibility, cost-effectiveness, and ability to provide immediate results ensure that they continue to be integral components of the oncological imaging arsenal (10).

3.2 Computed Tomography (CT)

Computed tomography (CT) has become a cornerstone in cancer diagnosis and management, revolutionizing the way tumors are visualized and assessed. CT scans provide detailed cross-sectional images of the body, allowing for accurate tumor localization, staging, and assessment of treatment response. This imaging modality is particularly useful in evaluating lung, liver, and pancreatic cancers, where precise anatomical information is crucial for effective treatment planning. One of the significant advantages of CT is its ability to generate high-resolution images that can

reveal the size, shape, and density of tumors. This information is essential for determining the extent of disease and identifying any potential metastases. The introduction of multidetector CT has further enhanced image quality and reduced scan times, making it a preferred modality for oncological imaging (11). Multidetector CT allows for the acquisition of multiple slices of data simultaneously, resulting in faster scans and improved spatial resolution. This advancement has made CT an invaluable tool in emergency settings, where rapid diagnosis is critical. CT imaging is also instrumental in assessing treatment response. By comparing pre- and post-treatment scans, clinicians can evaluate changes in tumor size and structure, providing valuable insights into the effectiveness of therapies such as chemotherapy and radiation. Additionally, CT-guided biopsies enable precise sampling of tumors, facilitating accurate histological diagnosis and allowing for the characterization of tumor types and subtypes (12). However, it is important to note that the use of CT involves exposure to ionizing radiation, which poses potential risks, particularly with repeated imaging. As a result, ongoing research is focused on optimizing CT protocols to minimize radiation exposure while maintaining diagnostic accuracy.

3.3 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is invaluable in the evaluation of soft tissue tumors, particularly in the brain, pelvis, and musculoskeletal system. Its superior contrast resolution allows for the differentiation of tumor types and assessment of tumor margins, which is critical for surgical planning. Unlike CT, MRI does not utilize ionizing radiation, making it a safer option for patients, particularly for those requiring multiple imaging studies over time (13).

MRI is particularly effective in characterizing brain tumors, where its ability to provide detailed images of soft tissues is unmatched. This capability allows for the identification of tumor types, assessment of surrounding structures, and evaluation of edema and other changes in the brain. In the pelvic region, MRI is the gold standard for assessing prostate and gynecological cancers, providing critical information about tumor size, location, and involvement of adjacent organs (14).

Functional MRI techniques, such as diffusion-weighted imaging (DWI) and perfusion MRI, provide additional information about tumor biology and treatment response. DWI measures the movement of water molecules within tissues, which can be altered in tumors due to changes in cellular density and structure. This technique has shown promise in differentiating between tumor types and assessing treatment response in various malignancies. Perfusion MRI evaluates blood flow to tumors, offering insights into tumor vascularity and metabolism. This information can be crucial in predicting treatment outcomes and guiding therapy decisions (15).

3.4 Positron Emission Tomography (PET)

PET imaging, often combined with CT (PET/CT), has revolutionized the assessment of cancer. It provides functional information about tumor metabolism, enabling early detection of malignancies and assessment of treatment efficacy (16). PET is particularly useful in lymphomas, lung cancer, and melanoma, where it aids in staging and monitoring response to therapy (17).

3.5 Ultrasound

Ultrasound plays a crucial role in cancer diagnosis, particularly for guiding biopsies and evaluating superficial tumors. It is a cost-effective and accessible imaging modality that provides real-time imaging without ionizing radiation (18). Ultrasound is commonly used in the assessment of breast, thyroid, and abdominal tumors.

4. The Role of Radiology in Cancer Staging and Treatment Planning

4.1 Staging

Accurate staging is essential for determining prognosis and treatment strategies. Radiology plays a pivotal role in the staging of cancer by providing detailed information about tumor size, location, and the presence of metastases. Imaging modalities such as CT, MRI, and PET are integral to the staging process, allowing for the classification of tumors according to established criteria, such as the TNM (Tumor, Node, Metastasis) system (19). This information is crucial for oncologists to develop appropriate treatment plans and to predict patient outcomes.

4.2 Treatment Planning

Radiology also contributes significantly to treatment planning. For surgical interventions, precise imaging is essential for identifying tumor margins and surrounding structures, which aids surgeons in achieving complete resection while minimizing damage to healthy tissue (20). In radiation therapy, imaging is used for treatment planning and verification, ensuring that radiation is delivered accurately to the tumor while sparing adjacent healthy tissues (21). Additionally, imaging plays a role in the selection of targeted therapies and immunotherapies by identifying specific tumor characteristics that may influence treatment decisions.

5. The Integration of Artificial Intelligence in Radiology

5.1 Overview of AI in Radiology

The integration of artificial intelligence (AI) and machine learning in radiology has the potential to transform cancer diagnosis and management. AI algorithms can analyze vast amounts of imaging data, identifying patterns and anomalies that may be missed

by human observers (22). This capability enhances diagnostic accuracy and efficiency, allowing radiologists to focus on complex cases that require their expertise.

5.2 Applications of AI in Cancer Imaging

AI applications in cancer imaging include automated detection of tumors, segmentation of lesions, and prediction of treatment response. For instance, deep learning algorithms have shown promise in detecting lung nodules on chest X-rays and CT scans, with performance comparable to that of experienced radiologists (23). Furthermore, AI can assist in radiomics by extracting quantitative features from images, which can be correlated with clinical outcomes and used to develop predictive models (24).

5.3 Challenges and Ethical Considerations

Despite the potential benefits of AI in radiology, several challenges must be addressed. These include the need for large, diverse datasets to train AI algorithms, the risk of algorithmic bias, and the importance of maintaining the radiologist's role in the diagnostic process (25). Ethical considerations surrounding patient privacy, data security, and the implications of AI-driven decision-making must also be carefully considered.

6. Future Directions in Radiology and Cancer Management

6.1 Emerging Imaging Technologies

The future of radiology in cancer diagnosis and management is poised for further advancements. Emerging imaging technologies, such as photoacoustic imaging and molecular imaging, offer the potential for enhanced sensitivity and specificity in tumor detection (26). These modalities may provide real-time information about tumor biology and microenvironment, facilitating more personalized treatment approaches.

6.2 Personalized Medicine and Radiology

The integration of radiology into personalized medicine is an exciting frontier. By combining imaging data with genomic and molecular information, clinicians can develop tailored treatment plans that consider the unique characteristics of each patient's tumor (27). This approach has the potential to improve treatment efficacy and minimize adverse effects.

6.3 Challenges Ahead

As the field of radiology continues to evolve, several challenges remain. The increasing volume of imaging data necessitates the development of efficient data management systems and standardized protocols for image acquisition and interpretation (28). Additionally, ongoing education and training for radiologists in

emerging technologies and AI applications will be essential to ensure that they remain at the forefront of cancer care.

7. Conclusion

The evolution of radiology in cancer diagnosis and management has been marked by significant technological advancements and a growing understanding of the role of imaging in patient care. From the early days of X-rays to the integration of AI and emerging imaging modalities, radiology has transformed the landscape of cancer diagnosis and treatment. As the field continues to advance, it is crucial to address the challenges and opportunities that lie ahead, ensuring that radiology remains a vital component of comprehensive cancer care.

References

1. Albertoni, P. , 2003. Novel antitenascin antibody with increased tumour localisation for pretargeted antibody-guided radioimmunotherapy (PAGRIT). *British Journal of Cancer* 88, 996–1003. [DOI] [PMC free article] [PubMed] [Google Scholar]
2. American College of Radiology, 2004. *Breast Imaging Reporting and Data System (BIRADS) fourth ed.* American College of Radiology; Reston, VA: [Google Scholar]
3. Anderson, H.L. , Yap, J.T. , Miller, M.P. , 2003. Assessment of pharmacodynamic vascular response in a phase I trial of combretastatin A4 phosphate. *Journal of Clinical Oncology* 21, 2823–2830. [DOI] [PubMed] [Google Scholar]
4. Aberg, P. , Nicander, I. , Hansson, J. , Geladi, P. , Holmgren, U. , Ollmar, S. , 2004. Skin cancer identification using multifrequency electrical impedance – a potential screening tool. *IEEE Transactions on Biomedical Engineering* 51, 2097–2102. [DOI] [PubMed] [Google Scholar]
5. Artemov, D. , Mori, N. , Okollie, B. , Bhujwalla, Z.M. , 2003. MR molecular imaging of the Her-2/neu receptor in breast cancer cells using targeted iron oxide nanoparticles.
6. *Magnetic Resonance in Medicine* 49, 403–408. [DOI] [PubMed] [Google Scholar]
7. Ashamalla, H. , Rafla, S. , Parikh, K. , Mokhtar, B. , Goswami, G. , Kambam, S. , 2005. The contribution of integrated PET/CT to the evolving definition of treatment volumes in radiation treatment planning in lung cancer. *International Journal of Radiation Oncology Biology Physics* 63, 1016–1023. [DOI] [PubMed] [Google Scholar]
8. Atri, M. , 2006. New technologies and directed agents for applications of cancer imaging.
9. *Journal of Clinical Oncology* 24, (20) 3299–3308. [DOI] [PubMed] [Google Scholar]
10. Backer, M.V. , 2007. Molecular imaging of VEGF receptors in angiogenic

- vasculature with single-chain VEGF-based probes. *Nature Medicine* 13, 504–509. [DOI] [PubMed] [Google Scholar]
11. Bae, U. , 2007. Ultrasound thyroid elastography using carotid artery pulsation. *Journal of Ultrasound in Medicine* 26, 797–805. [DOI] [PubMed] [Google Scholar]
12. Balamugesh, T. , 2005. Empyema – a rare complication of transbronchial lung biopsy. *Respiratory Medicine Extra* 1, (3) 97–99. [Google Scholar]
14. Bartella, L. , Huang, W. , 2007. Proton (1H) MR spectroscopy of the breast. *RadioGraphics* 27, S241–S252. [DOI] [PubMed] [Google Scholar]
15. Granata V., Fusco R., Filice S., Catalano O., Piccirillo M., Palaia R., Izzo F., Petrillo M. The current role and future perspectives of functional parameters by diffusion weighted imaging in the assessment of histologic grade of HCC. *Infect. Agents Cancer*. 2018;13:23.
16. doi: 10.1186/s13027-018-0194-5. [DOI] [PMC free article] [PubMed] [Google Scholar]
17. Granata V., Fusco R., Reginelli A., DelRio P., Selvaggi F., Grassi R., Izzo F., Petrillo A. Diffusion kurtosis imaging in patients with locally advanced rectal cancer: Current status and future perspectives. *J. Int. Med. Res.* 2019;47:2351–2360. doi: 10.1177/0300060519827168. [DOI] [PMC free article] [PubMed] [Google Scholar]
18. Fusco R., Granata V., Rega D., Russo C., Pace U., Pecori B., Tatangelo F., Botti G., Izzo F., Cascella M., et al. Morphological and functional features prognostic factor of magnetic resonance imaging in locally advanced rectal cancer. *Acta Radiol.* 2018 doi: 10.1177/0284185118803783. [DOI] [PubMed] [Google Scholar]
19. Bartella, L. , 2007. Enhancing non-mass lesions in the breast: evaluation with proton (1H) MR spectroscopy. *Radiology* 245, 80–87. [DOI] [PubMed] [Google Scholar]
20. Barthel, H. , 2003. 3'-Deoxy-3'-[18F]fluorothymidine as a new marker for monitoring tumor response to antiproliferative therapy in vivo with positron emission tomography. *Cancer Research* 63, 3791–3798. [PubMed] [Google Scholar]
21. Bauer, W. , Claudia, C. , Langer, O. , 2008. Microdosing studies in humans: the role of positron emission tomography. *Drugs in R & D* 9, (2) 73–81. [DOI] [PubMed] [Google Scholar]
22. Patterson DM, Padhani AR, Collins DJ. Technology insight: water diffusion MRI—a potential new biomarker of response to cancer therapy. *Nat Clin Pract Oncol.* 2008;5:220– 33. doi: 10.1038/ncponc1073. [DOI] [PubMed] [Google Scholar]
23. Lee KC, Bradley DA, Hussain M, et al. A feasibility study evaluating the functional diffusion map as a predictive imaging biomarker for detection of

- treatment response in a patient with metastatic prostate cancer to the bone. *Neoplasia*. 2007;9:1003–11. doi: 10.1593/neo.07954. [DOI] [PMC free article] [PubMed] [Google Scholar]
24. Kwee TC, Takahara T, Klomp DW, Luijten PR. Cancer imaging: novel concepts in clinical magnetic resonance imaging. *J Intern Med*. 2010;268:120–32. doi: 10.1111/j.1365-2796.2010.02243.x. [DOI] [PubMed] [Google Scholar]
 25. Kovacs A, Toth L, Glavak C, et al. Integrating functional MRI information into radiotherapy planning of CNS tumors—early experiences. *Pathol Oncol Res*. doi: 10.1007/s12253-010-9298-y. Epub ahead of print 2010 September 17. [DOI] [PubMed] [Google Scholar]
 26. Ng WH, Mukhida K, Rutka JT. Image guidance and neuromonitoring in neurosurgery. *Childs Nerv Syst*. 2010;26:491–502. doi: 10.1007/s00381-010-1083-4. [DOI] [PubMed] [Google Scholar]
 27. Scholar]
 28. Beyer T., Bidaut L., Dickson J., Kachelriess M., Kiessling F., Leitgeb R., Ma J., Sundar L.K.S., Theek B., Mawlawi O. What scans we will read: Imaging instrumentation trends in clinical oncology. *Cancer Imaging*. 2020;20:1–38. doi: 10.1186/s40644-020-00312-3. [DOI] [PMC free article] [PubMed] [Google Scholar]
 30. Vaidya T., Agrawal A., Mahajan A., Thakur M.H., Mahajan A., Aggarwal A. The Continuing Evolution of Molecular Functional Imaging in Clinical Oncology: The Road to Precision
 - i. Medicine and Radiogenomics (Part II) *Mol. Diagn. Ther*. 2018;23:27–51. doi: 10.1007/s40291-018-0367-3. [DOI] [PubMed] [Google Scholar]
 31. Mainenti P., Stanzione A., Guarino S., Romeo V., Ugga L., Romano F., Storto G., Maurea S., Brunetti A. Colorectal cancer: Parametric evaluation of morphological, functional and molecular tomographic imaging. *World J. Gastroenterol*. 2019;25:5233–5256. doi: 10.3748/wjg.v25.i35.5233. [DOI] [PMC free article] [PubMed] [Google Scholar]
 32. Moffat BA, Chenevert TL, Lawrence TS, et al. Functional diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response. *Proc Natl Acad Sci U S A*. 2005;102:5524–9. doi: 10.1073/pnas.0501532102. [DOI] [PMC free article] [PubMed] [Google Scholar]
 33. Mechtler L. Neuroimaging in neuro-oncology. *Neurol Clin*. 2009;27:171–201. doi: 10.1016/j.ncl.2008.09.015. [DOI] [PubMed] [Google Scholar]
 34. Hamstra DA, Chenevert TL, Moffat BA, et al. Evaluation of the functional diffusion map as an early biomarker of time-to-progression and overall survival in high-grade glioma. *Proc Natl Acad Sci U S A*. 2005;102:16759–64. doi: 10.1073/pnas.0508347102. [DOI] [PMC free article] [PubMed] [Google Scholar]
 35. article] [PubMed] [Google Scholar]