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THE IMPORTANCE OF IMAGING IN RADIATION THERAPY: A REVIEW ARTICLE

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Abstract

Radiotherapy is one of the modern cancer treatment modalities. Advances in medical technology have revolutionized external radiotherapy with CT scanning, allowing for the visualization and grouping of tumors and at-risk organs in a three-dimensional view. However, CT has some limitations, especially in assessing the character and delineation of tumors. PET and MRI go beyond CT in terms of functional and anatomical images. PET/CT/MRI multimodality combines the strengths of each technique without conflating their respective weaknesses, thereby strengthening the role of imaging for radiation therapy management. On account of this, it can become the primary technique in radiotherapy modalities. This review aims to describe multimodality of the PET/CT/MRI process for radiotherapy and its potential clinical applications.

Keywords: *Multimodality image, Radiotherapy, Co-registration CT/MRI/PET*

INTRODUCTION

There are many different modalities of modern cancer therapy. Radiation therapy is one of the backbones of cancer treatment today and has been recognized as an option for the management of various types of malignancies that are potentially curable. This can either be, by itself or in tandem with other medical procedures, for instance, surgery or chemotherapy. Radiation therapy can be successful if the tumor is wholly contained within the tissue volume treated with tumoricidal doses. Candidate patients who can be treated with curative or 'radical' radiation should have a localized extent of disease in an area that can be safely treated with tumoricidal doses. The exact location and extent of the tumor must be known to plan potentially curative radiation therapy.(1)

Precise radiation dose calculations have been developed to target volumes of nearly all malignancies. A new algorithm for three-dimensional (3D) dose calculation with a computer-based linear accelerator capable of transmitting an intensity-modulated radiation beam has made it possible to determine the radiation dose precisely.(2) External radiotherapy has evolved with the help of computed tomography (CT), which makes it possible to visualize and group tumors and organs at risk in a three-dimensional way. However, CT has some limitations, especially in characterizing and delineating tumors. Positron emission tomography (PET) and magnetic resonance imaging (MRI) are superior in functional and anatomical imaging, that is, over CT. The PET/CT/MRI trimodality is an association of the three.(3)

This review aims to describe the series of actions in the PET/CT/MRI trimodality along with its potential implementation in clinical practice.

1. RADIOTHERAPY

Radiotherapy is a treatment modality for both benign and malignant diseases and can be monotherapy or in combination with chemotherapy, surgery, or both. In addition, palliative radiotherapy is often used to reduce pain or the mass' effect in primary tumors or metastatic deposits. Therapeutic radiation can be administered from outside the patient, as external beam radiation therapy (EBRT), by implanting a radioactive source in a cavity or tissue (brachytherapy) or systemically through the administration of radiopharmaceutical agents. (4)

An essential first step in planning radiation treatment is delineating the target to determine the tumor area because accurate localization reduces the possibility of accidental exclusion of tumors from radiation exposure and allows maximal removal of normal tissue. Treatment begins with a radiation treatment planning simulation using computed tomographic (CT) images obtained while the patient is immobilized in a position deemed adequate. Magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) as complementary imaging studies can be incorporated electronically into a planning CT scan simulation or used as the primary imaging study for planning. Thus, complementary imaging techniques can be implemented in the treatment planning process. In addition, a margin of uninvolved, normal tissue adjacent to the tumor is often included in target imaging to account for variations in day-to-day patient settings and alignment, organ movement during treatment, and uncertainty about the extent of the disease. (4–6)

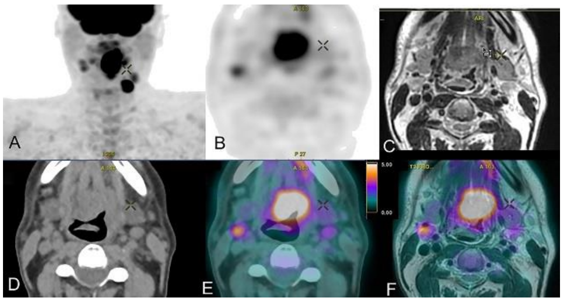

Figure 1. Trimodal acquisition of cancer of the base of the tongue in (A) the frontal maximum intensity projection PET image, (B) the axial PET FDG acquisition, (C) the axial T2 MRI acquisition, (D) the axial CT acquisition, (E) the axial PET/CT fusion, and (F) the axial PET/MRI fusion.(3)

2. MULTIMODAL IMAGING

2.1 CT scan

Computed tomography (CT) imaging is now recognized as the standard modality for image-based radiation therapy treatment planning and is used by radiation oncologists to determine the target and organ volumes at risk. CT is considered an imaging modality with a high spatial resolution. It provides spatially accurate data regarding human anatomy not affected by geometric distortion and portrays electron density mapping of the human tissue required for dosimetric calculations in radiotherapy. However, CT has certain drawbacks, such as a lack of contrast in soft tissues and artifacts due to the presence of metal (Table 1). (4,7)

CT imaging studies are registered via a laser-defined patient setting fiducial mark and are used to determine the anatomical structure and target volume from which the shape and orientation of the beam are planned. (4,7,8) CT can provide electron density information for heterogeneity-based dose calculations only if properly calibrated and free of image artifacts. (9)

2.2 MRI

MRI is a medical imaging technique that provides superior soft tissue contrast that can be both anatomical and functional. MRI also provides millimetric spatial resolution, which allows better differentiation between normal tissue and multiple tumors. Differentiating this contrast to metabolic and biochemical levels is also possible in the presence of magnetic resonance spectroscopy. Moreover, MRI is not limited to the acquisition of axial plane images.(4,9) Despite the advantages of non-irradiation, the acquisition process is time-consuming, and this technique presents many contraindications. The use of MRI as monotherapy for planning radiotherapy treatment will be limited by the lack of information about the electronic density of the tissue, the image intensity that is not constant, and the presence of geometric distortions that distort the image, including the desired volume. (3,10) Spatial distortion can alter the position of the target volume concerning anatomical landmarks. Other factors such as the patient's skin or external fiducial markers make MRI studies unsuitable for treatment planning (Table 1). (9)

2.3 PET

Positron emission tomography (PET) is a functional imaging modality that can provide excellent tumor/node contrast and the possibility of obtaining a wide field of view. (3) PET also provides unique information about the patient's physiology. PET has been used to evaluate tumor metabolism, differentiate tumor recurrence from radiation necrosis processes, evaluate regional lung function, detect hypoxic areas of the tumor, and perform other functional imaging. (9)

PET has limitations, including poor spatial resolution. As a result, this can result in inaccurate representations of the patient’s external contour as well as other normal structures. In addition, partial volume artifacts create blurred edges that make it difficult to segment the desired volume (Table 1).(3,9)

2.4 CT/MRI/PET Trimodality

Radiotherapy is relied on as the technique of choice in cancer treatment, and trimodality may offer anatomical and functional information depictions with a detailed spatial resolution and allow for increased definitions of the target volume in radiotherapy.(11,12)

Images of each modality should be performed in the radiotherapy treatment position, as the trimodality allows obtaining additional information about the disease and tumor. Each of the machines is fitted with a fixed table positioned above the device table. Each of these rigid tables has a marker and indexing system that allows the installation of a radiotherapy immobilization solution. Patient repositioning on each device was performed using markers on the skin (i.e., positioning reference) created during CT planning and an external positioning laser. (3,13)

Currently, no medical devices allow the acquisition of all three imaging modalities simultaneously. The solution uses two separate imaging devices, a bimodal hybrid engine, and an independent engine. Two trimodality systems are possible: PET/MRI coupled to planning CT (possibly with pseudo-CT generated from MRI for planning) or PET/CT coupled to MRI and then registered to plan for CT (possibly CT PET/CT if calibrated for radiotherapy). (3)

Data acquisition and processing solutions with PET/MR should be done with precautions considered. The patient is positioned on a device with an MR coil compatible with radiotherapy immobilization fixation. MR coil attenuation mapping must be performed beforehand to allow for the calibration of attenuation on the PET image. (3,14) The results of planning PET/MR and CT imaging are then registered prior to volume delineation and dosimetry planning. Another way to address these issues is by replacing CT planning with pseudo-CT, i.e., synthetic CT.(3,15) With artificial intelligence innovations, powerful new algorithms such as GAN (generative adversarial networks) allow the creation of attenuation maps and synthetic CT from different MR images. Thus, treatment planning can be carried out without proceeding to the imaging registration step.(16)

The second PET/CT + MRI approach is carried out through the same process; the patient undergoes the two tests in sequence in the position for the radiotherapy treatment. Two approaches may be implemented for this PET/CT + MRI workflow. The first one is by employing a transfer system appropriate to both instruments. This technique consists of a low-damping air cushion bed and a non-magnetic stretcher that makes it possible for the operator to move the bed from one instrument to the other without displacing the patient at all. The air cushion bed is placed on the fixed table of the first imaging instrument, and the patient is oriented in a position corresponding to the desired positioning reference for CT planning. After the first observation, the patient is transferred to a stretcher using a suction system and then transferred to the second imaging unit for imaging from the stretcher to the assessment table with the help of the same suction system. Ultimately, the system enables the implementation of a multimodal imaging system while maintaining the same position for the patient.(3,17)

For the second technique, PET/CT and MRI images are also performed in the radiotherapy planning condition but in the position of the patient standing between the two acquisitions. The patient is positioned on the first imager in the radiotherapy treatment condition using the markers defined during CT and external laser acquisition planning and continued under the same conditions to the second device. Image registration is the last step in the trimodality, where all acquisitions are placed in a common coordinate system. Image registration allows for the relationship of information from each modality to improve clinical interpretation.(3)

Image registration can be considered in two complementary approaches. The former is material-based and consists of carrying out all acquisitions under the same condition. First, the patient maintains the same position for each imaging procedure with the same immobilization system for radiotherapy.(18) The acquisition parameter will also allow for obtaining the best image alignment by keeping the table height and selecting equal slice thickness, the same plane extraction, or 3D acquisition with a wide field of view.(2)

This first approach accommodates the second approach, which is software-based. Image registration is done manually by a doctor, or assisted by an automated algorithm for image registration. For the second approach, evaluating beforehand the accuracy of the algorithm used is crucial. Several pieces of research have analyzed algorithms for CT-MRI or trimodality registration algorithms reporting that the mean error between 0.4 and 2 mm.(2,19) Finally, a special trimodality image fusion method may be considered for better delineating the target. However, visual validation remains important before proceeding with radiotherapy treatment planning. Image fusion is the final step in this trimodality process, linking information from each modality and improving clinical interpretation. In the multimodality context of radiotherapy, optimizing the acquisition parameters is a crucial step to facilitate image registration.(3)

Table 1. A Summary of the advantages and disadvantages of CT, MRI, and PET separately and combined as PET/CT/MRI trimodality.

MODALITY	Advantages	Disadvantages
CT	• Anatomy • Spatial resolution (1 mm) • Fast acquisition	• Irradiating • Contrast • Artifacts (metal, teeth, etc.)
MRI	• Anatomy and function • Spatial resolution (1 mm) • Contrast (Soft tissues) • Non-irradiating	• Long acquisition • Compatible MRI equipment with high-performance dedicated coils • Contraindications • Artifacts (Distortions, no uniformity, etc.)
PET	• Function • Tumor/Background Contrast • Acquisition field	• Irradiating • Spatial resolution (>3-4 mm) • Partial volume (blurred edges)
PET/CT/MRI Trimodality	• Anatomy and function • Spatial resolution • Tumor characterization • Assessment of disease spread • Dosimetry for RT	• Irradiating • Long acquisition • Image registration • Compatible MRI equipment with high-performance dedicated coils • Contraindications MRI

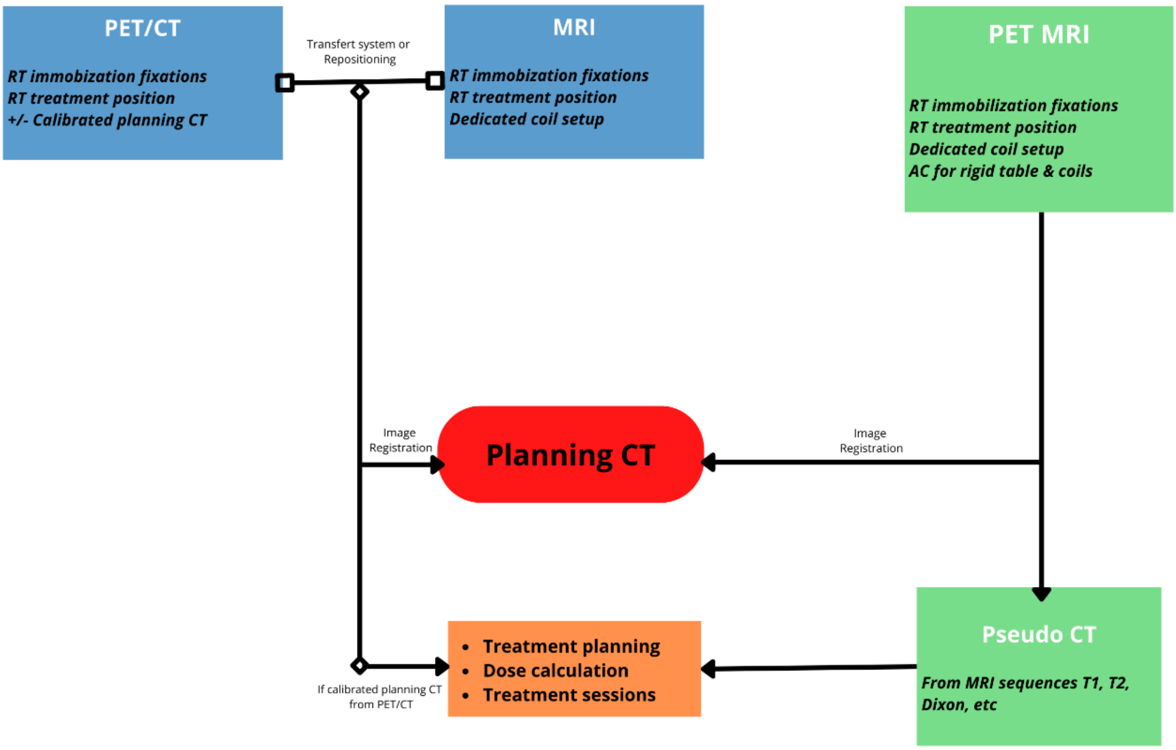

Figure 2. A diagram of performing the PET/CT/MRI trimodality in the radiotherapy treatment position.

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3. GAMMA KNIFE RADIOSURGERY

Gamma Knife radiosurgery (GKS) is a radiotherapy modality with the advantages of high conformity to intracranial tumors and sparing surrounding normal tissue from irradiation, thereby reducing radiation-related complications. However, due to inaccurate target delineation, GKS is often inadequate for achieving local control in patients with recurrent nasopharyngeal cancer (NPC). Therefore, an accurate depiction of tumor volume is essential to achieve better control with GKS. However, post-irradiation changes on MRI, such as edema, fibrosis, or tissue loss, can be confused with recurrent disease. Therefore, innovative GKS-related techniques such as co-registration with PET-CT and MRI should be considered to prevent such confusion.

The co-registration technique provides several advantages. One is clearer tumor margins compared to MRI or CT alone due to the co-registered PET-CT image technique. MRI is required to delineate tumor margins in GKS planning and is superior to CT; however, MRI contrast enhancement often makes it difficult to tell apart radiation-induced tumors, inflammation, and fibrosis. Second, the treatment plan can be customized so that the maximum radiation dose is applied to the "hot spots" identified on the PET-CT scan. Third, PET-CT for a treatment plan is valid for decision-making when the same modality will be used for follow-ups, especially in terms of identifying tumor recurrence and differentiating between malignant tissue and radiation necrosis.

The co-registration technique with PET/CT and MRI in GKS in recurrent NPC using the Model G Leksell Stereotactic Frame is applied to patients under local anesthesia. After attaching an imaging-compatible fiducial system to the frame, a high-resolution stereotactic MRI is performed. Images are then transferred to a computer workstation for treatment planning; stereotactic MR images are fused with PET-CT images using the co-registration technique. Recurrent NPC is outlined using optimized imaging integration of stereotactic MRI and conventional PET-CT.

4. CLINICAL APPLICATION

Radiation therapy requires accurate imaging as a key part of the treatment planning process for most malignancies that are managed with a curative purpose.(1) Trimodality has a high clinical impact and good observer agreement, especially for head and neck cancer, brain tumors, prostate cancer, and cervical cancer, and is already possible to do routinely clinically.(3)

Co-registration of various anatomical (e.g., CT and MRI) and functional (e.g., PET) images is a promising way to improve target volume imaging in planning head and neck tumor radiotherapy. Studies in patients with pharyngeal-laryngeal tumors imaged by CT scan, MRI (T1 and T2-weighted sequences), and PET (FDG transmission and emission) showed that co-registration accuracy was in the range of 0.8–6.2 mm and 1.2–4.6 mm for phantom and patient, respectively. Apart from that, the consistency is perfect except in the y direction. Thus, the study concluded that accurate co-registration of CT, MR, and F-fluorodeoxyglucose positron-emission tomography (FDG-PET) images could be obtained in the head and neck region.(2)

Integrating amino acid MRI and PET/CT can help increase gross tumor volume coverage in gliomas treated with 3D conformal radiotherapy, avoiding greater differences between physical and biological imaging techniques, especially for suspected areas of non-enlarging tumors. (10,20) In addition, 68Ga-DOTATOC PET, exploring SST2 receptor expression, could be useful in conjunction with CT and MRI for treatment planning for meningiomas, especially for detecting and assessing the extent of invasion of intracranial meningiomas and with impact on sparing normal tissue.(3,21)

A prospective study on the combination of PET PSMA and multiparametric MRI provided reliable TNM staging in patients with prostate cancer with changes in therapeutic management for nearly one-third of patients. PSMA PET is of great interest for delineating lymph node metastases. (22,23)

A cohort study of 134 patients has shown that MRI-guided intensity-modulated radiotherapy (IMRT) in combination with PET/CT-guided brachytherapy (IMRT) administered to primary cervical tumors correlates with local tumor control. However, imaging remains difficult because differences in tumor volume were observed between MRI and PET/CT. In addition, a prospective observational study involving 237 patients explored the role of MRI and FDG PET undertaken before, during, and after radiotherapy and chemotherapy.(3,24,25)

CONCLUSION

The key to planning radiotherapy for the treatment of malignancies is accurate imaging. The multimodality of PET/CT/MRI—combining the techniques' strengths and limiting each of their weaknesses—reinforces the role of imaging in guiding radiation therapy. Despite this recent multimodality, it is already possible to perform this routinely with high clinical impacts and good inter-observer agreement. However, additional clinical research is necessary to confirm the role of multimodality in clinical practices.

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REFERENCES

1. IAEA. The Role of PET/CT in Radiation Treatment Planning for Cancer Patient Treatment. Int At Energy Agency. 2008;
2. Daisne J-F, Sibomana M, Bol A, Cosnard G, Lonneux M, Grégoire V. Evaluation of a multimodality image (CT, MRI and PET) coregistration procedure on phantom and head and neck cancer patients: accuracy, reproducibility and consistency. Radiother Oncol [Internet]. 2003 Dec;69(3):237–45. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0167814003003876
3. Decazes P, Hinault P, Veresezan O, Thureau S, Gouel P, Vera P. Trimodality PET/CT/MRI and Radiotherapy: A Mini-Review. Front Oncol [Internet]. 2021 Feb 4;10. Available from: https://www.frontiersin.org/articles/10.3389/fonc.2020.614008/full
4. Citrin DE. Recent Developments in Radiotherapy. Longo DL, editor. N Engl J Med [Internet]. 2017 Sep 14;377(11):1065–75. Available from: http://www.nejm.org/doi/10.1056/NEJMra1608986
5. Bradley J, Thorstad WL, Mutic S, Miller TR, Dehdashti F, Siegel BA, et al. Impact of FDG-PET on radiation therapy volume delineation in non–small-cell lung cancer. Int J Radiat Oncol [Internet]. 2004 May;59(1):78–86. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0360301603022673
6. Li X, Zhang H, Xing L, Ma H, Xie P, Zhang L, et al. Mediastinal lymph nodes staging by 18F-FDG PET/CT for early stage non-small cell lung cancer: A multicenter study. Radiother Oncol [Internet]. 2012 Feb;102(2):246–50. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0167814011006281
7. Richard P, Sandison G, Dang Q, Johnson B, Wong T, Parvathaneni U. Dental amalgam artifact: Adverse impact on

tumor visualization and proton beam treatment planning in oral and oropharyngeal cancers. Pract Radiat Oncol [Internet]. 2015 Nov;5(6):e583–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1879850015001551

8. Herrmann H, Seppenwoolde Y, Georg D, Widder J. Image guidance: past and future of radiotherapy. Radiologe [Internet]. 2019 Dec 25;59(S1):21–7. Available from: http://link.springer.com/10.1007/s00117-019-0573-y

9. Mutic S, Dempsey J, Bosch W, Low D, Dryzmala R, Chao C. MULTIMODALITY IMAGE REGISTRATION QUALITY ASSURANCE FOR CONFORMAL THREE-DIMENSIONAL TREATMENT PLANNING. Int J Radiat Oncol Biol Phys. 2001;51(1):255–60.

10. Rundo L, Stefano A, Militello C, Russo G, Sabini MG, D'Arrigo C, et al. A fully automatic approach for multimodal PET and MR image segmentation in gamma knife treatment planning. Comput Methods Programs Biomed [Internet]. 2017 Jun;144:77–96. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0169260716300311

11. Yang J, Beadle BM, Garden AS, Schwartz DL, Aristophanous M. A multimodality segmentation framework for automatic target delineation in head and neck radiotherapy. Med Phys [Internet]. 2015 Aug 18;42(9):5310–20. Available from: http://doi.wiley.com/10.1118/1.4928485

12. Ak S, Kiliç C, Özlügedik S. Correlation of PET-CT, MRI and histopathology findings in the follow-up of patients with nasopharyngeal cancer. Braz J Otorhinolaryngol [Internet]. 2021 Nov;87(6):643–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1808869420300045

13. Reynaert N. PET and MRI based RT treatment planning: Handling uncertainties. Cancer/Radiothérapie [Internet]. 2019 Oct;23(6–7):753–60. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1278321819303105

14. Winter RM, Leibfarth S, Schmidt H, Zwirner K, Mönnich D, Welz S, et al. Assessment of image quality of a radiotherapy-specific hardware solution for PET/MRI in head and neck cancer patients. Radiother Oncol [Internet]. 2018 Sep;128(3):485–91. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0167814018302093

15. Wiesinger F, Bylund M, Yang J, Kaushik S, Shanbhag D, Ahn S, et al. Zero TE-based pseudo-CT image conversion in the head and its application in PET/MR attenuation correction and MR-guided radiation therapy planning. Magn Reson Med [Internet]. 2018 Oct;80(4):1440–51. Available from: https://onlinelibrary.wiley.com/doi/10.1002/mrm.27134

16. Peng Y, Chen S, Qin A, Chen M, Gao X, Liu Y, et al. Magnetic resonance-based synthetic computed tomography images generated using generative adversarial networks for nasopharyngeal carcinoma radiotherapy treatment planning. Radiother Oncol [Internet]. 2020 Sep;150:217–24. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0167814020303856

17. Veit-Haibach P, Kuhn FP, Wiesinger F, Delso G, von Schulthess G. PET–MR

imaging using a tri-modality PET/CT–MR system with a dedicated shuttle in clinical routine. Magn Reson Mater Physics, Biol Med [Internet]. 2013 Feb 9;26(1):25–35. Available from: http://link.springer.com/10.1007/s10334-012-0344-5

18. Lotterie J-A, Duthil P, Januel A-C, Redon A, Menegalli D, Blond S, et al. Imagerie stéréotaxique et diagnostique en radiochirurgie. Cancer/Radiothérapie [Internet]. 2012 Jun;16:S10–25. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1278321812000698

19. Wang X, Li L, Hu C, Qiu J, Xu Z, Feng Y. A comparative study of three CT and MRI registration algorithms in nasopharyngeal carcinoma. J Appl Clin Med Phys [Internet]. 2009 Mar;10(2):3–10. Available from: http://doi.wiley.com/10.1120/jacmp.v10i2.2906

20. Lohmann P, Stavrinou P, Lipke K, Bauer EK, Ceccon G, Werner J-M, et al. FET PET reveals considerable spatial differences in tumour burden compared to conventional MRI in newly diagnosed glioblastoma. Eur J Nucl Med Mol Imaging [Internet]. 2019 Mar 16;46(3):591–602. Available from: http://link.springer.com/10.1007/s00259-018-4188-8

21. Stade F, Dittmar J-O, Jäkel O, Kratochwil C, Haberkorn U, Debus J, et al. Influence of 68Ga-DOTATOC on sparing of normal tissue for radiation therapy of skull base meningioma: differential impact of photon and proton radiotherapy. Radiat Oncol [Internet]. 2018 Dec 2;13(1):58. Available from: https://ro-journal.biomedcentral.com/articles/10.1186/s13014-018-1008-z

22. Grubmüller B, Baltzer P, Hartenbach S, D'Andrea D, Helbich TH, Haug AR, et al. PSMA Ligand PET/MRI for Primary Prostate Cancer: Staging Performance and Clinical Impact. Clin Cancer Res [Internet]. 2018 Dec 15;24(24):6300–7. Available from: https://aacrjournals.org/clincancerres/article/24/24/6300/15407/PSMA-Ligand-PET-MRI-for-Primary-Prostate-Cancer

23. Walacides D, Meier A, Knöchelmann AC, Meinecke D, Derlin T, Bengel FM, et al. Comparison of 68 Ga-PSMA ligand PET/CT versus conventional cross-sectional imaging for target volume delineation for metastasis-directed radiotherapy for metachronous lymph node metastases from prostate cancer. Strahlentherapie und Onkol [Internet]. 2019 May 4;195(5):420–9. Available from: http://link.springer.com/10.1007/s00066-018-1417-9

24. Zhang S, Xin J, Guo Q, Ma J, Ma Q, Sun H. Comparison of Tumor Volume Between PET and MRI in Cervical Cancer With Hybrid PET/MR. Int J Gynecol Cancer [Internet]. 2014 May 1;24(4):744–50. Available from: https://ijgc.bmj.com/lookup/doi/10.1097/IGC.0000000000000097

25. Dyk P, Jiang N, Sun B, DeWees TA, Fowler KJ, Narra V, et al. Cervical Gross Tumor Volume Dose Predicts Local Control Using Magnetic Resonance Imaging/Diffusion-Weighted Imaging—Guided High-Dose-Rate and Positron Emission Tomography/Computed Tomography—Guided Intensity Modulated Radiation Therapy. Int J Radiat Oncol [Internet]. 2014 Nov;90(4):794–801. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0360301614035500