Review Article

Application of Multimodality Imaging Fusion Technology in Diagnosis and Treatment of Malignant Tumors under the Precision Medicine Plan

Shun-Yi Wang, Xian-Xia Chen, Yi Li, Yu-Ying Zhang

Department of Ultrasound, Qinghai People's Hospital, Xining, Qinghai 810007, China

Abstract

Objective: The arrival of precision medicine plan brings new opportunities and challenges for patients undergoing precision diagnosis and treatment of malignant tumors. With the development of medical imaging, information on different modality imaging can be integrated and comprehensively analyzed by imaging fusion system. This review aimed to update the application of multimodality imaging fusion technology in the precise diagnosis and treatment of malignant tumors under the precision medicine plan. We introduced several multimodality imaging fusion technologies and their application to the diagnosis and treatment of malignant tumors in clinical practice.
Date Sources: The data cited in this review were obtained mainly from the PubMed database from 1996 to 2016, using the keywords of "precision medicine", "fusion imaging", "multimodality", and "tumor diagnosis and treatment".
Study Selection: Original articles, clinical practice, reviews, and other relevant literatures published in English were reviewed. Papers focusing on precision medicine, fusion imaging, multimodality, and tumor diagnosis and treatment were selected. Duplicated papers were excluded.
Results: Multimodality imaging fusion technology plays an important role in tumor diagnosis and treatment under the precision medicine plan, such as accurate location, qualitative diagnosis, tumor staging, treatment plan design, and real-time intraoperative monitoring. Multimodality imaging fusion systems could provide more imaging information of tumors from different dimensions and angles, thereby offing strong technical support for the implementation of precision oncology.
Conclusion: Under the precision medicine plan, personalized treatment of tumors is a distinct possibility. We believe that multimodality imaging fusion technology will find an increasingly wide application in clinical practice.

Key words: Fusion Imaging; Magnetic Resonance Imaging; Multimodality; Precision Medicine; Tumor Diagnosis and Treatment

Introduction

The arrival of the precision medicine era brings new opportunities and challenges for patients undergoing precision diagnosis and treatment.[1] The morbidity and mortality rates associated with malignant tumors have increased year by year, and the burden of malignant neoplasms is increasing.[2-4] Therefore, precision oncology has become an important branch of precision medicine. Minimally invasive surgical treatment, minimally invasive treatment guided by imaging navigation, and specific therapy of targeted drugs are important aspects of precision oncology. With further development of medical imaging technology, information from different imaging modalities can be integrated and comprehensively analyzed by the imaging fusion system, which provides more image information of tumors from different angles and dimensions to accurately make qualitative and quantitative diagnoses and achieve the aim of precision tumor treatment. Multimodality image fusion technology has become the main trend in the development of future imaging technology.[5] This article reviews the application

Access this article online

Quick Response Code:

Website:
www.cmj.org

DOI:
10.4103/0366-6999.195467

Address for correspondence: Dr. Yu-Ying Zhang,
Department of Ultrasound, Qinghai People's Hospital, Xining,
Qinghai 810007, China
E-Mail: 1076208252@qq.com

Received: 12-08-2016 **Edited by:** Ning-Ning Wang
How to cite this article: Wang SY, Chen XX, Li Y, Zhang YY. Application of Multimodality Imaging Fusion Technology in Diagnosis and Treatment of Malignant Tumors under the Precision Medicine Plan. Chin Med J 2016;129:2991-7.

of several imaging fusion techniques in the diagnosis and treatment of tumors.

The Precision Medicine Plan and Multimodality Imaging Fusion Technology

In 2015, "the precision medicine initiative" proposed by the US had a profound impact all over the world.[6] Precision medicine is based on individual diagnosis and treatment; in essence, it analyzes and verifies the occurrence and development of diseases from a genetic and molecular level, thereby accurately identifying the cause of diseases and the target of drug action, to achieve maximum therapeutic effect and minimum adverse reactions.

Nowadays, malignant tumors are a global health concern; also, the morbidity and mortality rates associated with malignant disease have increased considerably in recent years.[4] Owing to the complexity of tumors and their development mechanisms, completely different genes may determine similar signs and symptoms while the same gene may cause different symptoms and signs. It has been observed that the "destructive" and "one size fits all" treatment methods for malignant tumors often result in a serious waste of medical resources, cause considerable economic burden to patients, and seriously affect patients' quality of life. Precision oncology is an important branch of precision medicine, that uses "individual treatment", has the advantage of causing less trauma, causing fewer complications, and offering good prognosis; therefore, precision oncology has become the cutting-edge field that needs prioritization in precision medicine.[7] Precision oncology must always consider three aspects of malignant tumors: prevention, diagnosis, and treatment, none of which is dispensable.[8] In the background of the current social medicine, any clinical method that can achieve individual diagnosis and treatment of malignant tumors, improve therapeutic effects, and reduce adverse effects belongs to the precision oncology.[9] Minimally invasive treatment guided by medical imaging navigation is one precise treatment method for malignant tumors.[10,11]

Medical imaging plays an important role in the qualitative and quantitative assessment of tumors, the precise and individual design of a surgical plan, and preoperative surgical simulation. While different imaging modalities provide diagnostic information at different levels, each imaging method has its own advantages, disadvantages, and specific indications.[12,13] Many types of imaging technologies complement each other to assist in precise qualitative and quantitative diagnosis of tumors and to achieve a more reasonable and comprehensive treatment plan.[14,15] The multimodality imaging fusion system takes contrastive analysis of the same lesion in different imaging modalities and provides more imaging information from different dimensions and angles; further, it uses a complementation assay and cross-validation to achieve accurate qualitative and quantitative diagnosis of tumors and offers a strong technical support for the implementation of precision oncology.[16]

Positron Emission Tomography/Computed Tomography Imaging Fusion Technology

Computed tomography (CT) is based on anatomical imaging while position emission tomography (PET) imaging is based on functional imaging that imparts information on tissue metabolism and physiological function. A PET/CT imaging fusion is, thus, an integration of functional and anatomical imaging at a cellular and molecular level, and it reflects the physiological and biochemical characteristics and anatomical structure of the diseased tissue.[17] PET/CT has an important guiding significance in tumor localization and qualitative diagnosis, tumor staging, tumor-biopsy-site selection, and development of radiotherapy planning.[18]

Precise localization and qualitative diagnosis of tumors

PET/CT can accurately locate tumors through high spatial resolution of CT; in addition, it can reflect the metabolic information of tumor cells to make an accurate judgment of the tumor's pathologic type. With only single PET imaging, it is difficult to precisely locate the tumor site; PET/CT fusion imaging improves the accuracy of tumor localization, especially in the head and neck region and for abdominal tumors.[19,20] PET/CT reduces the misdiagnosis and missed diagnosis rate of early-stage tumors, which can guide the choice of surgical methods and the resection scope of tumors, and also improve the quality of life for patients.[21]

A study[22] showed that PET/CT was highly accurate in characterizing indeterminate pulmonary nodules detected in lung cancer screening with low-dose CT, and it was helpful for the early diagnosis and treatment of lung cancer. Because there are various tumor types in the head and neck region, PET imaging alone is not sufficient to accurately locate these tumors. However, a PET/CT scan can provide precise positioning and qualitative diagnosis of such tumors. It is necessary to strictly control the radiation dose when planning radiotherapy for tumors in the head and neck region where are many important organs; moreover, precise delineation of gross tumor volume is the basis for reducing the radiation injury of normal tissue.[23] Hideghéty *et al.*[24] reported that PET/CT-based gross tumor volume delineation helped make modifications to radiotherapy planning in head and neck squamous cell carcinoma. The results showed that on the basis of the initial and post-ICT PET/CT comparison in 15/20 patients more than 50% volume reduction and in 6/20 cases complete response were achieved. Besides that, PET/CT is significantly valuable in monitoring tumor recurrence and distant metastasis. Suenaga *et al.*[25] reported that PET/CT had higher value in the surveillance of head and neck squamous cell carcinoma recurrence and distant metastasis than contrast-enhanced CT.

Determination of tumor stage and formulation of radiotherapy planning

The aim of most treatment methods is to maximally improve the local control rate of tumors and reduce the damage to normal tissue, while simultaneously increasing the cure rate of the tumor; precise staging plays a decisive role in formulating tumor-therapy strategies. A whole-body PET/CT scan can detect the existence of early lesions before morphological changes. PET/CT has the advantage of a large scanning range, and it can reveal tumor occurrence and metastasis in all tissues and organs and precisely locate the primary tumor and distant metastases. In addition, PET/CT can detect lymph node metastases measuring <1.0 cm in diameter anywhere in the body and help accurate TNM staging of tumors.[26-28] The purpose of radiotherapy is to provide the target area with an adequate curative radiation dose while exerting the least possible irradiation dose to the surrounding normal tissue. PET/CT can clearly indicate active regions of tumor metabolism and liquefaction of a necrotic area, in addition to accurately delineating tumor radiotherapy target volume that can help guide the radiation field and radiation dose distribution design, in order to prevent normal tissues from receiving unnecessary irradiation and improve the efficacy of tumor radiotherapy.[29,30] Nam *et al.*[31] reported that the PET/CT plan was better than the conventional point A plan in terms of target coverage without subjecting the normal tissue to an increased dose, which made optimized three-dimensional (3D) brachytherapy treatment planning possible. Whole-body PET/CT scans can also reduce missed diagnosis of metastatic lesions, help formulate individual treatment programs, and reduce the failure of locoregional therapy, thereby improving patient prognosis.

Accurate guidance of tumor-biopsy site

PET/CT functional imaging can show the most active part of tumor metabolism and locate it accurately during the process of sampling, such that components of liquefaction necrosis and secondary infection sites of tumors can be avoided. Further, it assists in obtaining biopsy samples from the most active part of the tumor to reduce false negative results. In addition, PET/CT can make use of tumor cell radiation concentration characteristics when biopsying the required sample before morphological changes, to aid in accurate early qualitative diagnosis of lesions and increase the cure rate of tumors.[32] Guo *et al.*[33] applied PET/CT-guided percutaneous biopsy with 51 patients of suspected lung cancer and bone metastases. The average biopsy time was 30 min. The results showed that the first-time diagnostic success rate of the biopsy was 96.1% (49/51), and the overall diagnostic success rate and sensitivity were both 100.0%; furthermore, no serious complications were encountered.

PET/CT imaging fusion technology has obvious advantages over magnetic resonance imaging (MRI), CT, radiography, and other single modality imaging techniques in tumor diagnosis and treatment, which can significantly reduce misdiagnosis and missed diagnosis rates, but PET/CT can also cause false negative and false positive results in tumor diagnosis. The imaging quality of PET/CT is affected by respiratory motion and it is easy to generate motion artifacts in the course of examination of thoracic tumors. To improve the quality of PET/CT fusion images, the selection of CT system still needs further clinical standardization; further, the methods to obtain a higher accuracy of PET/CT images should be addressed in further research studies.

Positron Emission Tomography/Magnetic Resonance Imaging Fusion Technology

PET/MRI fusion imaging can detect not only the anatomical, morphological, and functional information from MRI but also the cellular and physiological metabolism and molecular information from PET. MRI permits multi-sequencing and multi-parametric imaging. MRI has higher soft-tissue resolution than CT and causes no radiation damage. Compared with PET/CT, PET/MRI can achieve quasi-physiological synchronization and multi-functional information imaging. PET/MRI can provide more detailed tumor information and is likely more suitable for early screening and follow-up observation after treatment.[34]

PET/MRI has greater potential for qualitative diagnosis of early tumors than PET/CT, and it plays an important role in displaying local and/or distant lymph node metastasis and determining the TNM stage of tumors.[35] Integrative PET/MRI has both high soft-tissue resolution of MRI and high specificity of PET imaging, thus confirming that it has obvious advantages in the early diagnosis of head and neck tumors, breast cancers, and abdominal and pelvic tumors.[36,37] Heusch *et al.*[38] compared PET/MRI and PET/CT examination results and TNM staging in 22 patients with nonsmall cell lung cancer. Both imaging modalities showed consistent T-staging in 16 patients, and all 16 patients were correctly staged with respect to histopathology and N-staging. Overall, the accuracy of PET/MRI and PET/CT were 91% (20/22) and 82% (18/22), respectively, which indicated that PET/MRI had some advantages over PET/CT. Ohno *et al.*[39] reported that the accuracy of whole-body PET/MRI with signal intensity (SI) assessment was superior to that of PET/MRI without SI assessment and PET/CT, for identification of TNM classification, clinical stage, and operability evaluation of patients with tumors. Growing research suggests that PET/MRI could be a new positive noninvasive alternative approach as compared to PET/CT for tumor staging. In recent years, PET/MRI examination has also been used for the delineation of gross target volume in tumor radiotherapy, which provides a reliable means for the accurate estimation of tumor volume, and has achieved remarkable results.[40,41]

At present, the research of PET/MRI is still in its infancy, and there is a certain gap between clinical research and clinical promotion. In addition, PET/MRI is expensive and the imaging speed is slow, and both imaging modalities sometimes interfere with each other to influence the clarity and accuracy of the image. Besides, the operation of PET/MRI scanning requires an experienced radiologist while skilled and specialized physicians of medical imaging and nuclear medicine are typically scarce. However, despite this, PET/MRI examination has high application value in the diagnosis and treatment of tumors, especially for soft-tissue tumors.[42] When whole-body PET/MRI scan is used as a means of imaging fusion technology, it integrates functional imaging and cellular biological metabolism imaging and has great research potential for tumor biological characteristics and targeted therapy, tumor angiogenesis, and tumor tissue metabolism. With the development of an integrative system and improved attenuation correction technique, PET/MRI, as a kind of multimodality molecular imaging technology, has the potential to initiate a future revolution in tumor diagnosis and treatment.

Ultrasound-computed Tomography/Magnetic Resonance Imaging Fusion Technology

Precise and minimally invasive treatment of tumors is the development trend of clinical medicine, preoperative evaluation, and intraoperative monitoring. All postoperative evaluations of tumors require the support of imaging technology. Tissue biopsy guided by imaging technology improves the diagnostic accuracy, and imaging-guided tumor therapy is the embodiment of the individual and precise treatment of tumors. Ultrasound is the preferred imaging modality for puncture biopsy guidance and dynamic monitoring during operation of tumors, because of its convenience, real-time, high repeatability, and nonradiation. Ultrasound has its own shortcomings such as lack of spatial resolution, small imaging field, and many interference factors, whereas CT/MRI possesses high spatial resolution, larger imaging field, and less disturbances. Ultrasound-CT/MRI fusion technology achieves the integration of real-time ultrasound, convenience, and high spatial resolution and perfectly combines the advantages of different imaging modalities. At present, Ultrasound-CT/MRI fusion technology has become one of the research focuses in the field of interventional oncology.[43]

The spatial resolution of conventional ultrasound is low, and it is affected by gas, breathing movement, and body size. In addition, the ultrasonic wave produces attenuation in the process of transmission, hence making it difficult to access tumors in remote locations, leading to false negative results. With the development of multimodality ultrasound imaging technology, the diagnostic ability of ultrasound is also increasing.[44] However, ultrasound examination can still only poorly reveal tumors in isolated locations; therefore, tumor real-time puncture guidance, real-time monitoring of tumor ablation therapy, and other applications are limited. Ultrasound-CT/MRI fusion imaging brings a new entry point for puncture guidance and ablation monitoring of tumors, which are difficult to be visualize in single ultrasound examination.[45] First, locating tumors using CT/MRI scans and then making an alignment and fusion with real-time ultrasound examination that accomplishes real-time needle biopsy guidance for precise location puncture of isolated tumors, real-time ultrasound imaging can also be used to monitor tumor ablation under fusion imaging mode, which avoids damage to surrounding tissues.[46] Liu *et al.*[47] showed that all 18 target hepatocellular carcinoma (HCC) nodules could be detected with fusion images in all patients, but could not be detected on conventional ultrasound. The efficiency rate of microwave ablation assisted by real-time fusion imaging navigation system for HCCs undetectable by conventional ultrasound was 94.4% (17/18). It often needs multi-point repeated placement of electrode needles for larger tumors to achieve complete ablation. The atomization gas produced in the process of tumor ablation can interfere with the display of lesions, which is known to influence the accuracy of the subsequent needle arrangement, thereby leading to residual tumor and recurrence. At present, tumor radiofrequency ablation (RFA) often uses routine ultrasound examination for guidance. However, during the process of ablation, RFA requires an experienced operator to obtain the 3D anatomical imaging of tumors to make the needle arrangements and design the puncture route in his mind, which is poor of objectiveness. Ultrasound-CT/MRI fusion technology can be used to make a reasonable needle arrangement and design a suitable puncture route for the ablation of tumors by CT/MRI 3D reconstruction technology.[45] To reach minimum needle arrangement times and maximum ablation effect under the navigation of real-time Ultrasound-CT/MRI fusion imaging, the needle arrangement, needle insertion, and the ablation process should not be affected by the atomization gas. The operator subjective dependence is low, and the ablation process can be monitored in real time, which helps finally achieve the purpose of precise tumor ablation.[48]

Ultrasound-CT//MRI fusion imaging has an important significance in the evaluation of tumor ablation effect, detection of residual and recurrent tumor lesions, and guidance of re-treatment.[49] Conventional ultrasound examination cannot show tumor tissue micro blood flow perfusion. Although contrast-enhanced ultrasound (CEUS) can display real-time tumor micro blood flow perfusion, it is difficult to detect tumors with lack of blood flow using this imaging technique, owing to requirements of a highly skilled and experienced operator. Moreover, scanning range limits can easily lead to missed diagnosis, and hence, this method cannot accurately assess the tumor ablation effect. The tumor ablation process needs to inactivate not only the whole tumor tissue but also the surrounding 5 mm normal tissue, namely the ablation margin (AM). Reaching the AM or not is an independent risk factor for tumor recurrence. At present, no single modality imaging can accurately assess the AM. Fusion imaging technology can be used to fuse or compare the images obtained before and after tumor ablation, thus making the assessment of AM possible.[50] Mauri *et al.*[51] applied real-time virtual navigation system with Ultrasound-CT/MRI fusion imaging and found 295 liver tumors that were completely undetectable with nonenhanced ultrasound from 2002 to 2012. A total of 282 of 295 (95.6%) tumors were correctly targeted, and successful ablation was achieved in 266 of 295 (90.2%) tumors. This showed that Ultrasound-CT/MRI fusion imaging is precise for targeting and achieving successful ablation of target tumors undetectable with ultrasound alone. Song *et al.*[52] were able to detect 120 HCCs not visible on conventional ultrasound in 96 patients when fusion imaging was applied, and 38 (31.7%) of the 120 HCCs could be seen and RFA was feasible. Among the remaining 82 HCCs still not visible after image fusion, 26 (31.7%) were ablated under the guidance of fusion imaging, the technique based on peritumoral anatomic landmarks. Overall, 64 (53.3%) of 120 HCCs not visible on conventional ultrasound could be ablated under the guidance of the fusion imaging technique.

Ultrasound-CT/MRI fusion imaging can not only be used to evaluate whether the tumor ablation can reach the AM but also be used to assess the ablation effect in real time through CEUS. Once residual lesions are detected, ablation was carried out in a timely manner until the tumor completely disappeared; this reduces the recurrence rate of tumors and improves the prognosis of patients.[53]

The accuracy of Ultrasound-CT/MRI fusion imaging registration is affected by many factors such as patient posture and respiratory phase. To ensure the accuracy of registration, it is essential to maintain the same body position and breathing stage as far as possible during the CT/MRI scans. During ultrasound examination, the force applied by the operator should be gentle; otherwise, it will cause deformation of local tissue and affect the accuracy of image registration. The application of respiratory gating and motion tracking compensation technology in ultrasound examination has greatly improved the accuracy of image registration. Ongoing research indicates that ultrasound-3D ultrasound/CEUS based on ultrasound images for fusion will overcome complex operation, image-alignment difficulty, and other shortcomings as compared to Ultrasound-CT/MRI imaging fusion.[54] Imaging fusion with real-time ultrasound and new ultrasonic techniques will provide a more convenient, inexpensive, and precisely mediated platform for minimally invasive treatment of tumors.

Conclusions

Precision medicine plan brings new opportunities and challenges to the diagnosis and treatment of malignant tumors with advances both in the field of human genomics, metabolomics, and proteomics and considers data from other large-scale biological databases.

With our current understanding and background of medicine, methods of precision tumor treatment such as minimally invasive surgical treatment, minimally invasive interventional therapy, and targeted drug therapy are not possible without support from medical imaging. Multimodality medical imaging fusion technology has been widely applied in accurate tumor location, qualitative tumor diagnosis, tumor staging, treatment plan design, and real-time intraoperative monitoring. Multimodality medical imaging fusion technology will provide powerful technical support for the precise diagnosis and treatment of tumors in future clinical application. Currently, accurate registration and fusion method is still the most challenging aspect of imaging fusion technology. Further, interpretation of fusion imaging information is the main purpose of imaging fusion. Cultivating compound imaging talents is one of the challenges in fusion imaging technology. Finally, the selection of objective and optimal fusion imaging methods for different kinds of tumors is also a significant issue that needs to be addressed. With the continuous development of imaging and computer technology, multimodality imaging fusion technology will likely increasingly improve and mature with respect to fusion speed, stability, and accuracy. In addition, the development and application of multimodality contrast agents also opens new research avenues in multimodality imaging fusion technology.[55]

Multimodality fusion imaging brings more personalized and diversified diagnosis and treatment options to precision medicine, and these new diagnosis and treatment methods can accelerate the development of precision medicine.[56] Fusion imaging is very effective for tumor diagnosis and treatment. Therefore, the additional use of fusion imaging should be considered when single modality imaging is not satisfactory for tumor diagnosis and treatment.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Gunderson CC, Rowland MR, Wright DL, Andrade KL, Mannel RS, McMeekin DS, *et al.* Initiation of a formalized precision medicine program in gynecologic oncology. Gynecol Oncol 2016;141:24-8. doi: 10.1016/j.ygyno.2016.02.024.
2. Singh SD, Henley SJ, Ryerson AB. Surveillance for Cancer Incidence and Mortality – United States, 2012. MMWR Morb Mortal Wkly Rep 2016;63:17-58. doi: 10.15585/mmwr.mm6355a4.
3. Zheng R, Zeng H, Zhang S, Chen T, Chen W. National estimates of cancer prevalence in China, 2011. Cancer Lett 2016;370:33-8. doi: 10.1016/j.canlet.2015.10.003.
4. Allemani C, Weir HK, Carreira H, Harewood R, Spika D, Wang XS, *et al.* Global surveillance of cancer survival 1995-2009: Analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). Lancet 2015;385:977-1010. doi: 10.1016/S0140-6736(14)62038-9.
5. Panetta D, Marinelli M, Todiere G, Tripodi M, Salvadori PA, Neglia D. Hybrid imaging: Present and future of non-invasive diagnosis. Recenti Prog Med 2012;103:183-97. doi: 10.1701/1090.11981.
6. President Obama's State of the Union Address-Remarks as Prepared for Delivery. Available from: https://www.medium.com/@White-House/president-obamas-state-of-the-union-address-remarks-asprepared-for-delivery-55f9825449b2. [Last accessed on 2015 Jan 03].
7. Renfro LA, An MW, Mandrekar SJ. Precision oncology: A new era of cancer clinical trials. Cancer Lett 2016. pii: S0304-383530163-X. doi: 10.1016/j.canlet.2016.03.015.
8. Friedman AA, Letai A, Fisher DE, Flaherty KT. Precision medicine for cancer with next-generation functional diagnostics. Nat Rev Cancer 2015;15:747-56. doi: 10.1038/nrc4015.
9. Paparo F, Massollo M, Rollandi L, Piccardo A, Ruggieri FG, Rollandi GA. The clinical role of multimodality imaging in the detection of prostate cancer recurrence after radical prostatectomy and radiation therapy: Past, present, and future. Ecancermedicalscience 2015;9:570. doi: 10.3332/ecancer.2015.570.
10. Comaniciu D, Engel K, Georgescu B, Mansi T. Shaping the future

through innovations: From medical imaging to precision medicine. Med Image Anal 2016;33:19-26. doi: 10.1016/j.media.2016.06.016.
11. Frangi AF, Taylor ZA, Gooya A. Precision imaging: More descriptive, predictive and integrative imaging. Med Image Anal 2016;33:27-32. doi: 10.1016/j.media.2016.06.024.
12. Schulz A, Viktil E, Godt JC, Johansen CK, Dormagen JB, Holtedahl JE, *et al.* Diagnostic performance of CT, MRI and PET/CT in patients with suspected colorectal liver metastases: The superiority of MRI. Acta Radiol 2016;57:1040-8. doi: 10.1177/0284185115617349.
13. Ní Mhuircheartaigh JM, Siewert B, Sun MR. Correlation between the size of incidental thyroid nodules detected on CT, MRI or PET-CT and subsequent ultrasound. Clin Imaging 2016;40:1162-1166. doi: 10.1016/j.clinimag.2016.08.006.
14. Michallek F, Dewey M. Fractal analysis in radiological and nuclear medicine perfusion imaging: A systematic review. Eur Radiol 2014;24:60-9. doi: 10.1007/s00330-013-2977-9.
15. O'Connor JP, Rose CJ, Waterton JC, Carano RA, Parker GJ, Jackson A. Imaging intratumor heterogeneity: Role in therapy response, resistance, and clinical outcome. Clin Cancer Res 2015;21:249-57. doi: 10.1158/1078-0432.CCR-14-0990.
16. Wang XL, Li K, Su ZZ, Huang ZP, Wang P, Zheng RQ. Assessment of radiofrequency ablation margin by MRI-MRI image fusion in hepatocellular carcinoma. World J Gastroenterol 2015;21:5345-51. doi: 10.3748/wjg.v21.i17.5345.
17. Jung NY, Kim SH, Kang BJ, Park SY, Chung MH. The value of primary tumor (18) F-FDG uptake on preoperative PET/CT for predicting intratumoral lymphatic invasion and axillary nodal metastasis. Breast Cancer 2016;23:712-7. doi: 10.1007/s12282-015-0629-4.
18. Zheng Y, Sun X, Wang J, Zhang L, DI X, Xu Y. FDG-PET/CT imaging for tumor staging and definition of tumor volumes in radiation treatment planning in non-small cell lung cancer. Oncol Lett 2014;7:1015-1020. doi: 10.3892/ol.2014.1874.
19. Staniuk T, Malkowski B, Srutek E, Szlezak P, Zegarski W. Comparison of FLT-PET/CT and CECT in gastric cancer diagnosis. Abdom Radiol (NY) 2016;41:1349-56. doi: 10.1007/s00261-016-0647-5.
20. Ouyang L, Shi ZY, Lin ZG. 18F-FDG PET/CT makes a significant contribution to diagnosis of malignancy in patients with cervical lymphadenopathy: A study using optimal scale regression tests. Chin Med J 2013;126:659-67. doi: 10.3760/cma.j.issn.0366-6999.20121483.
21. Wu J, Aguilera T, Shultz D, Gudur M, Rubin DL, Loo BW Jr., *et al*. Early-stage non-small cell lung cancer: Quantitative imaging characteristics of (18)F fluorodeoxyglucose PET/CT allow prediction of distant metastasis. Radiology 2016;281:270-8. doi: 10.1148/radiol.2016151829.
22. Garcia-Velloso MJ, Bastarrika G, de-Torres JP, Lozano MD, Sanchez-Salcedo P, Sancho L, *et al.* Assessment of indeterminate pulmonary nodules detected in lung cancer screening: Diagnostic accuracy of FDG PET/CT. Lung Cancer 2016;97:81-6. doi: 10.1016/j.lungcan.2016.04.025.
23. Manca G, Vanzi E, Rubello D, Giammarile F, Grassetto G, Wong KK, *et al.* (18)F-FDG PET/CT quantification in head and neck squamous cell cancer: Principles, technical issues and clinical applications. Eur J Nucl Med Mol Imaging 2016;43:1360-75. doi: 10.1007/s00259-015-3294-0.
24. Hideghéty K, Cserháti A, Besenyi Z, Zag L, Gaál S, Együd Z, *et al*. Role of 18FDG-PET/CT in the management and gross tumor volume definition for radiotherapy of head and neck cancer; single institution experiences based on long-term follow-up. Magy Onkol 2015;59:103-10.
25. Suenaga Y, Kitajima K, Ishihara T, Sasaki R, Otsuki N, Nibu K, *et al.* FDG-PET/contrast-enhanced CT as a post-treatment tool in head and neck squamous cell carcinoma: Comparison with FDG-PET/non-contrast-enhanced CT and contrast-enhanced CT. Eur Radiol 2016;26:1018-30. doi: 10.1007/s00330-015-3902-1.
26. Huellner MW, de Galiza Barbosa F, Husmann L, Pietsch CM, Mader CE, Burger IA, *et al.* TNM staging of non-small cell lung cancer: Comparison of PET/MR and PET/CT. J Nucl Med 2016;57:21-6. doi: 10.2967/jnumed.115.162040.
27. Lee SM, Park CM, Paeng JC, Im HJ, Goo JM, Lee HJ, *et al.* Accuracy and predictive features of FDG-PET/CT and CT for diagnosis of lymph node metastasis of T1 non-small-cell lung cancer manifesting as a subsolid nodule. Eur Radiol 2012;22:1556-63. doi: 10.1007/s00330-012-2395-4.
28. Xu N, Wang M, Zhu Z, Zhang Y, Jiao Y, Fang W. Integrated positron emission tomography and computed tomography in preoperative lymph node staging of non-small cell lung cancer. Chin Med J 2014;127:607-13. doi: 10.3760/cma.j.issn.0366-6999.20131691.
29. Berberoglu K. Use of Positron Emission Tomography/Computed Tomography in radiation treatment planning for lung cancer. Mol Imaging Radionucl Ther 2016;25:50-62. doi: 10.4274/mirt.19870.
30. Zaffino P, Ciardo D, Piperno G, Travaini LL, Comi S, Ferrari A, *et al.* Radiotherapy of Hodgkin and non-Hodgkin lymphoma: A nonrigid image-based registration method for automatic localization of prechemotherapy gross tumor volume. Technol Cancer Res Treat 2016;15:355-64. doi: 10.1177/1533034615582290.
31. Nam H, Huh SJ, Ju SG, Park W, Lee JE, Choi JY, *et al.* 18F-fluorodeoxyglucose positron emisson tomography/computed tomography guided conformal brachytherapy for cervical cancer. Int J Radiat Oncol Biol Phys 2012;84:e29-34. doi: 10.1016/j.ijrobp.2012.02.055.
32. El-Haddad G. PET-based percutaneous needle biopsy. PET Clin 2016;11:333-49. doi: 10.1016/j.cpet.2016.02.009.
33. Guo W, Hao B, Chen HJ, Zhao L, Luo ZM, Wu H, *et al.* PET/CT-guided percutaneous biopsy of FDG-avid metastatic bone lesions in patients with advanced lung cancer: A safe and effective technique. Eur J Nucl Med Mol Imaging 2016;43:1-8. [Epub ahead of print]. doi: 10.1007/s00259-016-3455-9.
34. Ishii S, Shimao D, Hara T, Miyajima M, Kikuchi K, Takawa M, *et al.* Comparison of integrated whole-body PET/MR and PET/CT: Is PET/MR alternative to PET/CT in routine clinical oncology? Ann Nucl Med 2016;30:225-33. doi: 10.1007/s12149-015-1050-y.
35. Sotoudeh H, Sharma A, Fowler KJ, McConathy J, Dehdashti F, *et al.* Clinical application of PET/MRI in oncology. J Magn Reson Imaging 2016;44:265-76. doi: 10.1002/jmri.25161.
36. Tabouret-Viaud C, Botsikas D, Delattre BM, Mainta I, Amzalag G, Rager O, *et al.* PET/MR in breast cancer. Semin Nucl Med 2015;45:304-21. doi: 10.1053/j.semnuclmed.2015.03.003.
37. Moon SH, Yang BY, Kim YJ, Hong MK, Lee YS, Lee DS, *et al.* Development of a complementary PET/MR dual-modal imaging probe for targeting prostate-specific membrane antigen (PSMA). Nanomedicine 2016;12:871-9. doi: 10.1016/j.nano.2015.12.368.
38. Heusch P, Buchbender C, Köhler J, Nensa F, Gauler T, Gomez B, *et al.* Thoracic staging in lung cancer: Prospective comparison of 18F-FDG PET/MR imaging and 18F-FDG PET/CT. J Nucl Med 2014;55:373-8. doi: 10.2967/jnumed.113.129825.
39. Ohno Y, Koyama H, Yoshikawa T, Takenaka D, Seki S, Yui M, *et al.* Three-way comparison of whole-body MR, coregistered whole-body FDG PET/MR, and integrated whole-body FDG PET/CT imaging: TNM and Stage Assessment Capability for non-small cell lung cancer patients. Radiology 2015;275:849-61. doi: 10.1148/radiol.14140936.
40. Leibfarth S, Mönnich D, Welz S, Siegel C, Schwenzer N, Schmidt H, *et al.* A strategy for multimodal deformable image registration to integrate PET/MR into radiotherapy treatment planning. Acta Oncol 2013;52:1353-9. doi: 10.3109/0284186X.2013.813964.
41. Leibfarth S, Eckert F, Welz S, Siegel C, Schmidt H, Schwenzer N, *et al.* Automatic delineation of tumor volumes by co-segmentation of combined PET/MR data. Phys Med Biol 2015;60:5399-412. doi: 10.1088/0031-9155/60/14/5399.
42. Ruhlmann V, Ruhlmann M, Bellendorf A, Grueneisen J, Sawicki LM, Grafe H, *et al.* Hybrid imaging for detection of carcinoma of unknown primary: A preliminary comparison trial of whole-body PET/MRI versus PET/CT. Eur J Radiol 2016;85:1941-7. doi: 10.1016/j.ejrad.2016.08.020.
43. Tyson MD, Arora SS, Scarpato KR, Barocas D. Magnetic resonance-ultrasound fusion prostate biopsy in the diagnosis of prostate cancer. Urol Oncol 2016;34:326-32. doi: 10.1016/j.urolonc.2016.03.005.
44. Opielinski KJ, Pruchnicki P, Gudra T, Podgórski P, Kurcz J, Krasnicki T, *et al.* Imaging results of multi-modal ultrasound computerized tomography system designed for breast diagnosis. Comput Med Imaging Graph 2015;46(Pt 2):83-94. doi: 10.1016/j.Compmedimag.2015.02.004.
45. Diana M, Halvax P, Mertz D, Legner A, Brulé JM,

Robinet E, *et al.* Improving echo-guided procedures using an ultrasound-CT image fusion system. Surg Innov 2015;22:217-22. doi: 10.1177/1553350615577483.
46. Wu W, Xue Y, Wang D, Li X, Xue J, Duan S, *et al.* Application of 3D imaging in the real-time US-CT fusion navigation for minimal invasive tumor therapy. Int J Comput Assist Radiol Surg 2015;10:1651-8. doi: 10.1007/s11548-015-1224-z.
47. Liu FY, Yu XL, Liang P, Cheng ZG, Han ZY, Dong BW, *et al.* Microwave ablation assisted by a real-time virtual navigation system for hepatocellular carcinoma undetectable by conventional ultrasonography. Eur J Radiol 2012;81:1455-9. doi: 10.1016/j.ejrad.2011.03.057.
48. Minami Y, Kudo M. Ultrasound fusion imaging of hepatocellular carcinoma: A review of current evidence. Dig Dis 2014;32:690-5. doi: 10.1159/000368001.
49. Kang TW, Rhim H. Recent advances in tumor ablation for hepatocellular carcinoma. Liver Cancer 2015;4:176-87. doi: 10.1159/000367740.
50. Tomonari A, Tsuji K, Yamazaki H, Aoki H, Kang JH, Kodama Y, *et al.* Feasibility of fused imaging for the evaluation of radiofrequency ablative margin for hepatocellular carcinoma. Hepatol Res 2013;43:728-34. doi: 10.1111/hepr.12022.
51. Mauri G, Cova L, De Beni S, Ierace T, Tondolo T, Cerri A, *et al.* Real-time US-CT/MRI image fusion for guidance of thermal ablation of liver tumors undetectable with US: Results in 295 cases. Cardiovasc Intervent Radiol 2015;38:143-51. doi: 10.1007/s00270-014-0897-y.
52. Song KD, Lee MW, Rhim H, Cha DI, Chong Y, Lim HK. Fusion imaging-guided radiofrequency ablation for hepatocellular carcinomas not visible on conventional ultrasound. AJR Am J Roentgenol 2013;201:1141-7. doi: 10.2214/AJR.13.10532.
53. Toshikuni N, Tsutsumi M, Takuma Y, Arisawa T. Real-time image fusion for successful percutaneous radiofrequency ablation of hepatocellular carcinoma. J Ultrasound Med 2014;33:2005-10. doi: 10.7863/ultra.33.11.2005.
54. Park HJ, Lee MW, Rhim H, Cha DI, Kang TW, Lim S, *et al.* Percutaneous ultrasonography-guided radiofrequency ablation of hepatocellular carcinomas: Usefulness of image fusion with three-dimensional ultrasonography. Clin Radiol 2015;70:387-94. doi: 10.1016/j.crad.2014.12.003.
55. Sun Y, Zhu Y, Huang C, Li R, Chen Y, Duan Y, *et al.* Magnetite loaded polypeptide-PLGA multifunctional microbubbles for dual-mode US/MR imaging. Contrast Media Mol Imaging 2016;11:146-53. doi: 10.1002/cmmi.1675.
56. Shaikh F, Jacob A, Van Gestel F, Yaghoubi S. Molecular imaging in genetic medicine. Cureus 2016;8:e565. doi: 10.7759/cureus.565.