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REVIEW ARTICLE

Fusion imaging: a bipartite approach

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Abstract Image fusion is the process of registering and combining multiple images from single or multiple imaging modalities to improve the imaging quality and applicability. It reduces randomness and redundancy to increase the diagnostic value of images for better assessment of medical problems. Fusion imaging was designed to overcome the disadvantages of morphological and/or functional imaging, and attempts to provide inputs that improve treatment planning, resulting in better prognostication. This review attempts to summarize the techniques and their applications in head and neck imaging.

Keywords Anatomic imaging · Functional imaging · Fusion imaging · PET-CT · PET-MR

Introduction

Dental radiology has long played an exciting and critical diagnostic role in dentistry, and this has never been truer than now with the rapidly expanding array of available imaging modalities. Based on simple intraoral periapical radiography, several medical imaging modalities have been introduced in recent times, and continue to be developed at a phenomenal rate. Meanwhile, totally, new imaging techniques have also been introduced, and the resolution and image quality of existing systems are continually being refined and improved. Research and development have focused on manipulating and altering all three of the basic requirements for image production: the patient, the image-generating equipment (finding alternatives to ionizing radiation), and the image receptor.

Each diagnostic modality has distinct advantages and disadvantages, and thus, attempts are being made to combine two or more techniques to deliver better results [1]. The combinations aim to provide both anatomic and functional information about the region of interest, thereby enriching the clinical implications [2]. Advanced imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), permit exact anatomic delineation of lesions from surrounding structures, and aid in analyzing internal structures of lesions. However, these techniques fail in the detection of metastatic lymph nodes and prediction of responses to chemoradiation. Molecular imaging in its broadest definition represents methodologies that allow visualization of events at the cellular or molecular level and permit biologic imaging [3]. Signals from various intracellular targets, such as cell surface receptors, transporters, intracellular enzymes, or mRNAs, are evaluated. Estimation of the biological nature of a lesion, including its cellularity, growth rate, and response to different treatment regimens, may play an invaluable role in diagnosis, prognostication, and treatment planning [4].

The combination (fusion) of two imaging techniques, developed in recent years, is known as coregistration, hybrid technique, or fusion imaging [5]. The aim of this review is to summarize the existing modalities for fusion imaging of the head and neck and their clinical applications. Image fusion is the process of aligning and superimposing images obtained by two different imaging modalities under specific conditions [6]. By uniting metabolic function with anatomic form, fusion imaging depicts the human body with a new level of precision.

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According to James et al. [7], “Medical image fusion is the process of registering and combining multiple images from single or multiple imaging modalities to improve the imaging quality and reduce randomness and redundancy to increase the clinical applicability of medical images for diagnosis and assessment of medical problems”.

Radiological interpretation of certain clinical situations can be tricky, wherein the role of fusion imaging becomes crucial [8]. Interpretation of images is complicated when contrast perfusion (monitoring of a contrast agent through the microvasculature after injection) is disrupted by prior surgery or radiotherapy that can lead to tissue damage or necrosis, meaning that the contrast patterns can mimic those associated with neoplasia. In turn, this makes it difficult to define the anatomic extent of disease, which is necessary for planning of highly conformal radiation treatment or highly targeted therapeutic regimens [9].

Historical review

Hasegawa and colleagues are to be credited for the conception and design of the first combined SPECT/CT unit in the 1990s [10, 11]. Following this, many other eminent physicists and scientists have paved the way toward the modern era of fusion imaging. In 1998, Townsend and coworkers at the University of Pittsburgh pioneered the development of a combined PET/CT imaging system, with the capability of recording both PET emission and X-ray transmission data for correlated functional/structural imaging [12, 13]. Recently, compact and cost-effective designs for dual-modality systems have been established with the goal of offering a more economic approach to multimodality imaging for institutions with limited resources.

Diagnostic imaging modalities

Anatomic imaging

Imaging modalities, such as CT and MRI, reflect the normal anatomy and anatomic changes. Delineation of organs and structures is enhanced with the use of contrast agents. Despite these advances, in tissues with similar densities, normal and pathological tissues cannot be differentiated with good sensitivity and specificity, because there is little information on the metabolic activity of organs and lesions, e.g., detection of metastases in normal-size lymph nodes. These modalities can only detect cancers when they are ≥ 1 cm in diameter, i.e., when they consist of $>10^9$ cells. The advantages and disadvantages of various anatomic imaging modalities are summarized in Table 1.

Functional imaging

Evolution of imaging modalities that can assess the biologic domain of lesions can help toward better understanding of lesion pathophysiology and allow better evaluation of treatment strategies. Molecular imaging detects changes at the cellular level, early in the disease course, before structural changes can even be seen on CT/MRI [14]. Thus, such techniques may permit customization of treatment and better prognostication. Molecular imaging helps in determining the extent/severity of disease, selection of therapy, efficacy of a particular regimen, assessment of disease progression, and identification of recurrence. Differentiation of viable malignant tissue or active infection from normal tissue and nonviable remnants can be achieved by functional

Table 1 Anatomic imaging modalities

	Imaging modality	Advantages	Disadvantages	Fusion modalities
1	Magnetic resonance imaging	Soft issue is imaged with high accuracy No exposure to radiation	Sensitive to movement Longer scan time	Ultrasound-MRI MRI-CT MRI-PET MR-SPECT
2	Computed tomography	Short scan time High imaging resolution	Limited tissue characterization because of nature of X-ray source	MRI-CT SPECT-CT Ultrasound-CT FDG-PET-CT
3	Cone-beam computed tomography	Short scan time Lower radiation exposure	Low image quality Unreliable density measurements	CBCT-PET MR-CBCT
4	Ultrasound imaging	Cost-effective No exposure to radiation Easy access	Inferior morphological assessment Significant interobserver and intraobserver variability	Ultrasound-MRI Ultrasound-CT MRIgFUS Real-time virtual sonography

imaging with 18-fluorodeoxyglucose (^{18}F-FDG-PET) scanning [15]. Other tracers help in visualizing important parameters, such as DNA synthesis, mitotic activity, protein synthesis, local ischemia, and expression of tumor-specific receptors [16]. However, the major drawbacks of PET scanning are the relatively low spatial resolution of images and poor recognition and delineation of anatomic structures [17, 18]. Advanced MRI techniques, such as dynamic MRI and MR spectroscopy (MRS), also show functional aspects, such as vascularity, blood perfusion, oxygenation, and biochemical information. Moreover, MRI contrast agents have been developed to label specific tissues. The advantages and disadvantages of various molecular imaging modalities are summarized in Table 2.

Combined imaging

When fused, the anatomic information derived from CT/MRI and the functional information generated by PET provide better detail about the lesion in question. Thus, fusion imaging improves the diagnostic value beyond the sum of the individual modalities. The three major areas of focus in studies on image fusion [19–21] are: (a) identification, improvement, and development of imaging modalities useful for image fusion; (b) development of different techniques for image fusion; and (c) application of image fusion to human organs of interest for assessment of medical conditions.

Advantages of fusion imaging [22–24]

1. Provides structural and functional information in the same image.
2. Accurate identification of tumor/metastasis margins, enabling better tumor staging. The technique also permits a better identification of small recurrent tumors obscured by scar tissue at sites of radiation or postoperative necrosis.
3. Identification of lymph node metastasis or small tumor areas missed by CT/MRI.
4. Differentiation of active sites in an anatomically undiscernible lesion, thus improving the reading efficiency.
5. Detection of large tumors lying in clinically inaccessible areas, such as the hypopharynx or maxilla.
6. Locating the primary lesion in cases with unknown primary tumors.
7. Helps in treatment planning, guidance of biopsy, surgery, or radiation therapy, and prognostication.
8. Improves confidence in diagnosis when one modality alone is not definitive.
9. Permits quantification of differences between scans.

Disadvantages of fusion imaging [22, 24]

1. Resultant image may be less clear than the parent images.
2. Lower spatial resolution and greater degradation of spectral resolution.
3. Image distortion, such as ringing artifact or blocking effect, may be inherent.
4. High cost and low availability.
5. Blurring may affect contrast of the image.
6. Complexity of the procedure.
7. Majority of techniques are still in experimental stages and need refinement.
8. Limitations imposed by specific imaging modalities or nature of the clinical problem.

Applications of fusion imaging

The information provided by anatomic and molecular imaging modalities has spurred the development of various strategies for multimodality image registration and fusion that are currently used in clinical practice.

1. PET-CT/PET-MR [24]. (a) Used for detection of osseous metastases. (b) Has the extra advantage of detecting occult primary, associated visceral, and unsuspected metastases in addition to osseous metastases. (c) Used for assessment of metabolic activity in malignant lesions, and evaluation of staging, treatment response, and long-term prognostication. (d) PET-MR is particularly helpful for excluding residual disease and identifying candidates for salvage surgery after chemoradiation. (e) PET-MR is useful for delineation of gross tumor volume in radiotherapy in oral and oropharyngeal cancers. (f) PET-CT is superior to CT/MRI for detecting occult cervical node metastases.
2. A ^{68}Ga-DOTA-NOC scan is used to identify tumors expressing somatostatin receptors, the most common being neuroendocrine tumors [25].
3. ^{18}F-choline is used to identify lesions with high contents of choline (cell membrane proliferation marker), similar to MRS [26].
4. ^{18}F-angiography can be used to assess neovascularization of tumors, similar to CT and MR perfusion. CT and MR perfusion scans are technically limited, because a whole body scan is not possible [27].
5. Epilepsy and dementia imaging. Among the neurological diseases, CT and MRI detect unsuspected clinically significant lesions in only 5% of patients with dementia. Hypometabolic areas of the brain can be epileptogenic foci in the interictal phase on ^{18}F-FDG-PET imaging. These foci can be better localized on

Table 2 Molecular imaging modalities

	Technique	Principle and advantages	Disadvantages	Applications
1	Positron emission tomography (PET)	Transport of radiolabeled glucose into cells High sensitivity	Low resolution (better than SPECT) Cannot differentiate inflammatory sites from neoplastic processes Chance of false-positives (brown fat, infection, asymmetric muscle activity) and false-negatives (small tumor, low glycolytic activity)	Permits evaluation of residual or recurrent disease after treatment Allows treatment response assessment, but may only be valid at 10–14 weeks after completion of treatment Aids in gross tumor volume contouring and biology-guided adaptive radiation therapy planning
2	Single photon emission computed tomography (SPECT)	Nuclear medicine tomographic imaging using gamma-rays or characteristic X-rays	Poor resolution Time-consuming Underestimation is possible in deep tissues through absorption of gamma-rays	Detection of condylar hyperplasia Presence of metastatic lesions Prognostication in jaw osteonecrosis and cancer Evaluation of mandibular growth in asymmetries
3	Proton MR spectroscopy	Detects presence of specific metabolites (elevated Cho/Cr levels suggest higher membrane turnover) in tissues	Low signal-to-noise ratio	Benign neck tumors Differentiates between malignant and benign salivary gland tumors Evaluation of residual and recurrent tumors following treatment (early prediction possible) Has potential to predict response
4	Computed tomographic perfusion (CTP)	Continuous recording of X-ray attenuation over fixed area of interest during passage of a fast bolus of iodinated contrast medium through the region Evaluates blood volume, blood flow, mean transit time, and capillary permeability of a lesion Reproducible technique	Requires injection of contrast medium Large exposure to radiation	Differentiates malignant lesions from benign lesions Differentiation of recurrent tumor from post-therapy changes Predicts response to chemoradiation Non-invasive measurement of intratumoral MVD (risk factor for local recurrence, shorter disease-free survival, and distant metastases)
5	Perfusion-weighted MRI	Blood flow dynamics at microcirculation level Similar to CTP	Paramagnetic contrast medium injection Longer scan time Difficulty in optimization	Differentiates tumors from normal tissues
6	Diffusion-weighted imaging (DWI)	Tissues that are more compact at the molecular level (e.g., tissues with higher cellularity) tend to show relative reduction of water molecular motion expressed as lower ADC values Reproducible images in any MRI protocol	Lack of optimized threshold ADC values Susceptibility to dental fillings causing magnetic artifacts	Differentiates benign lesions from malignant lesions Evaluation of post-radiation therapy xerostomia Recurrent tumors show decreased ADC compared with non-malignant changes or radionecrosis Predicts response to chemoradiation (tumors with lower DC values respond better)

Table 2 (continued)

	Technique	Principle and advantages	Disadvantages	Applications
7	Diffusion tensor imaging (DTI) Form of DWI	Characterizes 3-D diffusion of water Tracks nerves from adjacent structures Characterizes microstructural changes	Nonspecific marker of neuropathology, thus imposing diagnostic or therapeutic challenges	Still in experimental stages Future applications may be related to salvage of important structures during surgery
8	Hypoxia (optical-based, MRI-based, or PET imaging-based)	PET-based potential tumor hypoxia imaging agents include ^{18}FFMISO and copper 60 (II)-diacetyl-bis (N4-methylthiosemicarbazone)	Suboptimal imaging Poor resolution	Crucial for prognostication of tumors (predicting aggressiveness, metastatic spread, and rate of recurrence) Response to chemoradiation
9	Cell proliferation (PET-based)	Injected 3′-deoxy-3′-F-18-fluorothymidine becomes concentrated in nucleosides	Tumor vs. normal tissue contrast is low Less marrow uptake	Differentiates tumor activity from inflammation caused by radiation Lymph node detection Reduction in proliferative activity of primary tumor
10	Inhibition of tumor neoangiogenesis	^{18}F-galacto-RGD-PET imaging of avB3 expression, a receptor related to tumor angiogenesis and metastasis		Planning and response evaluation of avB3-targeted therapies

high-resolution MRI fused with PET scans. In addition, MR-tractography images can be fused with PET images as well as routine MRI to demonstrate foci of white matter and grey matter hypertrophy corresponding to hypometabolic areas on PET [28].

6. Fusion imaging with color Doppler and MRI in cardiac imaging can extend the field of view in echocardiography and display both anatomic and hemodynamic information, thus improving the information derived with either modality alone [29].
7. Infection and inflammation. Among the usual imaging modalities, CT is the typical choice for detection of osseous involvement, while MRI is preferred for soft-tissue involvement because of its superior soft-tissue contrast and higher sensitivity to tissue edema and hyperemia. In nuclear medicine studies, several agents are used for detection of sites of infection and inflammation, the commonest being indium-111, technetium-99m (^{99m}Tc)-labeled leukocytes, and gallium-67 citrate [30–32].

Process of fusion imaging

The two stages of any classical image fusion method are: (1) image registration and (2) fusion of relevant features from the registered images. Image registration requires a method to correct any spatial misalignment between the different image data sets, and often involves compensation of variability resulting from scale changes, rotations, and translations [33].

Levels of image fusion

In reading two imaging studies, such as PET and CT, three levels of image fusion are possible: visual, software, and hardware fusion.

Visual fusion [34]

The reviewer traditionally has a film print or digital display of a previously recorded CT scan next to the PET images and overlays the images in their mind while performing the review. This is called visual fusion. Based on clinical experience, Jager et al. [35] estimated that there was a need to look at CT images in only about 20% of cases. They also stated that, in the majority of these cases, visual fusion gave sufficient information with no actual need for or additional value from software or hardware image fusion.

Software-based image registration and fusion [36]

For exceptional digital communication in medicine (through digital imaging and communication in Medicine-DICOM) connectivity, compatibility between various imaging modalities is required for software-based image registration and fusion, which can be challenging to perform.

Two main strategies are followed to perform rigid registration, as described in the following:

Identification of similar structures in the two images and subsequent minimization of a "distance measure" between these structures.

Voxel-for-voxel measuring of the full three-dimensional data for matching. The criterion that drives this registration algorithm is known as the "similarity measure". These approaches include minimization of histogram dispersion, maximization of mutual information, or maximization of correlation ratio.

The various fusion techniques following software fusion are described in the following.

MR-CT imaging [37]

Procedure MR images are initially acquired after immobilizing the patient, followed by acquisition of CT images. The two types of images are then integrated through automatic fusion by the software using anatomic structures. The fused images permit a better tumor volume evaluation [34].

Uses This modality is used for gross tumor volume delineation in oral and oropharyngeal cancer. It was reported that each system has certain inaccuracies, such as streak artifacts, partial volume effects, similar densities of healthy and malignant tissue on CT, and need for heterogeneity on MRI. Improved soft-tissue contrast, better craniocaudal resolution, and no streak artifacts or radiation are the strong points of MRI. When both modalities were used, MRI was found to be better for visualization of soft-tissue borders and bone-marrow invasion, while CT provided a better visualization of tumor–fat boundaries and bone cortex invasion.

Real-time virtual sonography (RVS) [37–39]

Procedure This technique enables the display of ultrasound (US) B/color Doppler images and CT/MR images in real time. The system includes a magnetic positioning sensor fixed on the probe of the US scanner, to create images with identical cross sections in real time. This is achieved by the position and angle of the probe in relation to previously acquired CT and MRI volume data. To display virtual images, it is necessary to transfer the CT or MRI data to the US machine. The workstation monitor displays two images: US real-time image and virtual reconstructed CT/MR multiplanar reconstruction image.

Uses This RVS module is used for radiofrequency ablation and assessment of tumor angiogenesis.

Combined US-CT imaging/hybrid ultrasonographic techniques

Procedure Registration of CT data to intraprocedural US images is carried out using specific anatomic and topographical landmarks during real-time US examination [5]. Magnetic tracking devices are installed in both the US probe and the ablation electrode. An electromagnetic tracking system, composed of a transmitter and a small receiver (mounted on the US probe), provides the position and orientation of the US probe in relation to the transmitter. This permits correct representation in size and orientation of the second modality image. Preoperative CT data are incorporated before ablation by manual registration. However, CT examination with such fusion imaging modalities must meet the following requirements:

Volume data must be archived in the DICOM format.

Slice thickness should be 3 mm or less and reconstruction images should have the same thickness.

CT scan area must include some standard anatomic structures, such as the xiphoid process.

Uses The use of tracked US, alongside multimodal registration of US to preoperative CT data, has huge potential for improving ablation treatments [40]. Many uncertainties regarding intraoperative tumor localization and delivery can be removed by precisely mapping the preoperative and planning data into the coordinate system of the live US during the actual procedure.

Hardware-based multimodality imaging

The images are acquired using special equipment designed for the purpose, with the patient undergoing both imaging procedures in sequence. The individual images and fusion images are all available for later evaluation. The images are interpreted by both radiologists and nuclear medicine physicians who can view the CT images, PET images, and fused PET/CT data, followed by preparation of the associated clinical report (Figs. 1, 2, 3).

Combined PET/CT instrumentation [41]

Procedure Dual-modality imaging systems are available to record CT and PET examinations sequentially. The patient

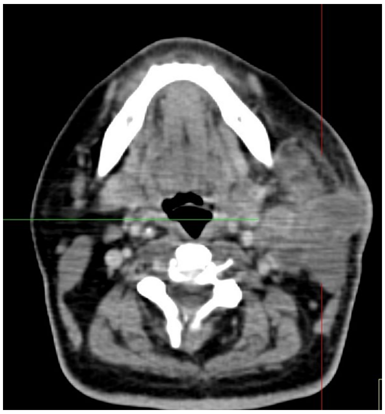

Fig. 1 Plain axial CT demonstrating a soft-tissue mass in the *left* parotid region

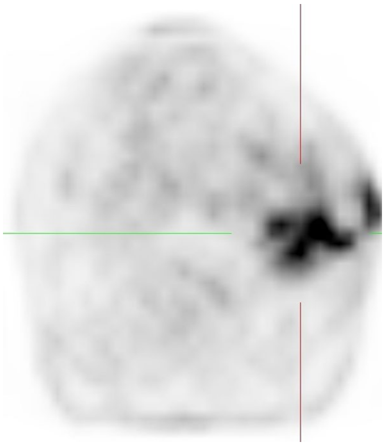

Fig. 2 PET scan of the same patient showing hot spots in the tumor mass, suggestive of high metabolic activity

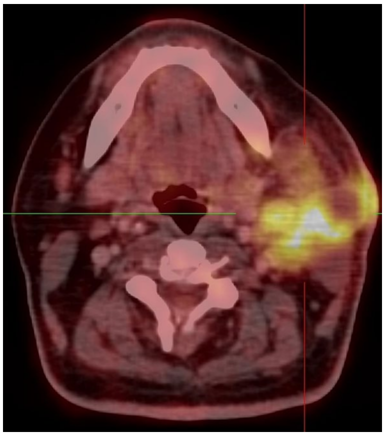

Fig. 3 Fused PET-CT image providing both anatomic and functional detail

is positioned on the table of the dual-modality imaging system and undergoes an "overview" or "scout" image to identify the axial extent of the CT and PET examinations. The patient then undergoes low-dose spiral CT acquisition, followed by the PET examination starting at approximately 1 h after FDG administration. The CT and PET data are reconstructed and registered, with the CT data used for attenuation correction of the reconstructed PET images. In some cases, contrast-enhanced CT is used to correct the PET data for photon attenuation, and the low-dose CT scan is no longer needed.

Uses Functional imaging using dynamic contrast-enhanced CT or MRI sequences may allow improved knowledge of head and neck squamous tumors. PET may allow further physiological information to be determined.

1. ^{18}F-FDG-PET-CT utilizes the fact that activated mononuclear cells and neutrophilic granulocytes are associated with infection-respiratory bursts (large quantities of glucose being utilized through hexose monophosphate shunts), resulting in higher FDG uptake in infection sites. Besides this, physiologic FDG uptake in the hematopoietic marrow is relatively low, making PET-CT a promising imaging technique for acute as well as chronic non-osseous and osseous inflammatory and infectious diseases.
2. FDG-PET-CT appears to be useful for differentiating disk space infection and erosive degenerative disk disease, wherein both MRI and ^{99m}Tc bone scans may give false-positive readings.
3. In soft-tissue infections, discrimination of active infectious lesions from residual changes arising from curative processes or postoperative changes can be detected at an early stage by PET-CT.

Combined PET/MRI instrumentation [42, 43]

Procedure In early MRI-compatible PET units, photomultiplier tubes (PMTs) were kept at a reasonable distance from the strong magnetic field of the clinical MRI unit. The detectors were coupled to long optical fibers (4–5 m), leading the weak scintillation light outside the fringe magnetic field to position-sensitive PMTs. Subsequent investigators developed PET/MRI systems with suitable solid-state detectors that can be operated within the magnetic field for PET imaging. These systems include avalanche photodiodes (APDs) and Geiger-mode avalanche photodiodes (G-APDs).

Uses These systems are being assessed in clinical settings to exploit the full potential of anatomic MRI in terms of high soft-tissue contrast sensitivity, in addition to the many other possibilities offered by this modality, such as blood oxygenation level-dependent (BOLD) imaging, functional MRI, diffusion-weighted imaging, perfusion-weighted imaging, and diffusion tensor imaging. Hybrid PET/MRI scanners combine the high soft-tissue contrast of MRI with the molecular and/or metabolic information of PET.

MRI-cone-beam computed tomography (CBCT)

Although MRI-CBCT fused images are slightly more limited than CBCT images alone for detection of osseous abnormalities, use of fused images has improved consistency among examiners in detecting disk positions relative to the condyle [44].

CBCT-PET

This integration is being tried for image-guided radiotherapy protocols and is in the experimental stages. The accuracy is comparable to that of CT-PET.

MRI-guided focused US surgery (MRIgFUS) [45]

Procedure This involves the combination of two technologies: MRI and ultrasonography. Ultrasonography uses a precisely-focused high-power acoustic beam to detect focused tissue necrosis by protein denaturation and capillary bed destruction. Meanwhile, MRI serves as an excellent imaging modality that provides three-dimensional images.

Uses Al-Hille et al. [46] reported that MRIgFUS can ablate soft-tissue tumors in bone. It is very effective for pain palliation in a single treatment, especially for painful metastases, and can be repeated in case of pain recurrence. The therapy also has great potential for combination with radiation.

The combination of these technologies has led to a breakthrough in image-guided therapy delivery systems, and fulfills the requirement of “ideal surgery”. The various advantages of this technique over other surgical treatments are as follows:

1. It requires no incision.
2. It has no bio-effects. Focused US permits concentrated US energy to be delivered into deep-seated tissues, without thermal effects on the surrounding tissues.
3. It can be repeated multiple times, whenever necessary.
4. Thermal ablations can be monitored by the temperature sensitivity of MRI.
5. It provides a precise definition of the targeted tumor volume, compared with actual visual inspection after surgery.
6. It is a better imaging modality for tumor localization or any soft-tissue pathology, compared with US or CT.
7. It does not require an aggressive approach.
8. It can be used for debulking of cancerous tissue.

Conclusions

Image fusion is the process of combining relevant information from a set of images into a single image, wherein the fused image becomes more informative and complete, and has increased applications compared with the input images. Although fusion imaging already has wide clinical applications in oncology, refinement of the existing techniques for a wide array of practical applications may serve to further expand the current fusion imaging protocols and applications.

Compliance with ethical standards

Conflict of interest Aravinda Konidena, Samridhi Shekhar, Avani Dixit, Deepa Jatti Patil, and Rajesh Gupta declare that they have no conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. The manuscript does not contain identifying information of patients.

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