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RESEARCH ARTICLE

HYBRID IMAGING: A COMPLEMENTARY EFFECT ON HEAD AND NECK ONCOLOGY

*Dr. Nikhat Mukhtar Gazge, Dr. Balaji, P., Dr. Sowbhagya, M. B. and Dr. Yogesh Pawar

Department of Oral Medicine and Radiology, Rajarajeswari Dental College and Hospital, #14 Ramohalli Cross, Mysore Road, Bangalore – 560074, Karnataka, India

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ABSTRACT

It is well known that cross-sectional anatomical imaging techniques such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) etc. have important roles in non-invasive diagnosis and in tumour treatment strategies. Likewise, nuclear medicine procedures such as positron emission tomography (PET) and single photon emission computerized tomography (SPECT) are unparalleled in their ability to assess information about metabolic function. Despite their advantages over conventional imaging, they have their own limitations in oncologic imaging. These limitations can be overcome by combining anatomical and functional imaging techniques. These techniques have different working principles and consequently complement each other with respect to the information obtained. The combination (fusion) of two imaging techniques has been developed in recent years, defining the so-called "hybrid techniques'' or "fusion imaging". Combinations of anatomical imaging techniques (ultrasound with CT or MR imaging), as well as associations between anatomical (CT or MR imaging) and molecular (SPECT or PET) imaging modalities are currently being used in clinical practice. This paper highlights the fusion of various imaging modalities and their applications in the arena of head and neck cancers.

INTRODUCTION

From advances in X-ray films and cassettes to introduction of computers and digital images, diagnostic imaging has never stopped reinventing its technology to improve patient care. Today, diagnostic imaging is on the cusp of explosive growth in an arena known as "Fusion imaging". This technology merges two independent imaging modalities- one, that demonstrates an organ's anatomy and the other that demonstrates the organ's function- to produce a diagnostically and clinically superior diagnostic study. Currently, fusion imaging has found its application in many areas of medicine. However, this review paper highlights the clinical applications of fusion imaging in head and neck cancers.

Methods of image fusion

Image fusion can be performed at 3 different levels:

1. Visual fusion
2. Software fusion
3. Hardware fusion

In traditional visual image fusion, the physician compares 2 separate imaging modalities viewed next to each other and the fusion takes place in his or her mind. Interpreting images obtained on two different modalities side by side is time consuming and logistically demanding. It also results in diagnostic inaccuracy because of imperfect anatomical matching (Becker and Zaidi, 2014). The software technique uses anatomic landmarks to coregister images from separate CT or MRI scanners to the images acquired from PET or SPECT. Softwares (Figure 1) for image fusion have been developed by various vendors and is universally applicable to all sorts of image sets. It provides evaluation of 2 modalities in 1 integrated image set. Currently, the software technique is more common because it is less expensive and more readily available.

Until recently radiologists had to obtain physiological and anatomical information on separate machines and use special registration softwares to digitally superimpose the two images. Today, hybrid equipment are available that are capable of performing both types of examination simultaneously, automatically merging the data to form a composite image (Clarke *et al*., 2002). The scanners for the different imaging modalities are combined within the same equipment. This makes it possible to sequentially acquire SPECT/PET and CT/MRI in a single imaging session. By uniting metabolic function with anatomic form, fusion imaging depicts the human body with a level of precision never achievable before with fusion of clinically significant anatomic and metabolic data.

Corresponding author: Dr. Nikhat Mukhtar Gazge,
Department of Oral Medicine and Radiology, Rajarajeswari Dental College and Hospital, #14 Ramohalli Cross, Mysore Road, Bangalore – 560074, Karnataka, India.

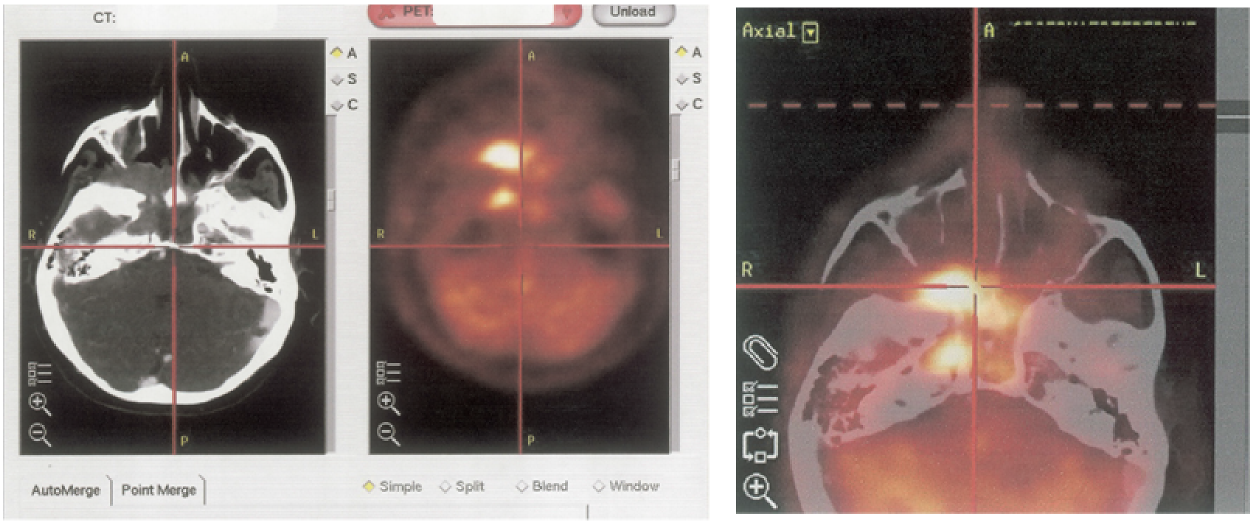

Figure 1.

The first commercial system to combine functional and anatomic imaging capabilities was a SPECT-CT unit introduced commercially in 1998. In 1999, manufacturers began working on Hybrid PET-CT system and the first commercial PET-CT unit was introduced in 2000 (Clarke *et al*., 2002). Several ultrasound systems for fusion imaging of real-time ultrasound with CT or MRI or PET/CT are commercially available. All systems are based on an electromagnetic tracking system—a transmitter and a small sensor mounted on the ultrasound probe— that provides the position and orientation of the transducer in the transmitter's spatial volume. The previously recorded CT or MRI or PET/CT or MRI dataset is transferred to the ultrasound system, and a coregistration from external or internal markers is performed. Afterward, the CT, MRI, or PET/CT or MRI dataset is reformatted in a projection to fit the real-time ultrasound image. The images may be shown side by side or superimposed (Ewertsen *et al*., 2013).

Application of fusion imaging in Head and Neck cancer

Head and neck cancer is the sixth most common cancer in the world with approximately 640,000 cases per year with approximately 350,000 deaths per year (Ghosh, 2012). With such a significant prevalence, oncologic imaging plays an important role in head and neck cancers. The imaging findings can aid significantly in detection, staging, restaging, and therapy response assessment of these tumours. Accurate staging at the time of diagnosis is critical for selection of the appropriate treatment strategy. After therapy, early detection of recurrence is also critical to achieve an optimal outcome. Imaging modalities such as Computerized tomography (CT), Magnetic resonance imaging (MRI) are superior at depicting normal anatomy and anatomic changes. They are the standard conventional imaging modalities for evaluation of patients with head and neck cancer (El-Khodary *et al*., 2011). These anatomic imaging modalities, however, are based on morphologic diagnostic criteria, such as nodal size and contrast enhancement patterns that do not always accurately reflect the presence of active malignancy. Moreover, they may be unable to differentiate between normal and pathologic tissues with similar densities. They provide relatively little information about the viability or metabolic activity of organs and lesions, thus lacking sufficient sensitivity and specificity to answer a number of important clinical questions. Well-known examples are the differentiation of viable tumour from scar tissue after external beam radiation or chemotherapy and the detection of metastases in normal-size lymph nodes. The regional anatomy is distorted by surgery and/or radiation making the distinction between post-treatment changes and recurrence or residual tumour difficult with imaging tests (El-Khodary *et al*., 2011). Hence, anatomical imaging modalities have a limited accuracy in response assessment after treatment of head and neck cancers as well as early diagnosis of recurrence.

On the other hand, nuclear medicine procedures such as positron emission tomography (PET) and single photon emission computerized tomography (SPECT) are unparalleled in their ability to assess information about metabolic function. Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET), a functional imaging modality, is based on its capability to assess the metabolic status of tumours. It permits the differentiation of viable malignant tissue or active infection from normal tissue and from nonviable remnants by direct visualization of metabolic activity in vivo. Other tracers currently under development may prove useful in visualizing other important parameters, such as DNA synthesis, mitotic activity, protein synthesis, local ischemia, and expression of tumour-specific receptors. Thallium-201 (201Tl) SPECT has unique features that enable it to reveal metabolically active tissue by virtue of its cellular uptake by malignant cells. PET and SPECT are superior to CT and MRI in diagnosing and differentiating recurrence from post radiation effects and surgical scars in sites of tumours of the head and neck and also in the detection of cervical lymph node status in cases of head and neck cancer. However, they are limited by the lack of anatomic landmarks, and the precise localization of suspicious findings is difficult due to the low background tracer uptake.[5]Despite high contrast resolution, their major drawbacks are the relatively low spatial resolution of images (at present in the range of 4–6 mm and physically limited to about 2 mm), poor recognition and delineation of anatomic structures. This may result in uncertainty or even failure in correctly localizing detected abnormalities. In addition, variable degrees of physiologic and inflammatory non cancer-related uptake of FDG in the region of the head and neck mainly after treatment can confound interpretation of suspicious foci (El-Khodary *et al*., 2011). As rightly said by Sir Stephen Wainwright, “Structure without function is a corpse… and function without structure is a ghost”. The limitations in separate anatomic and functional imaging may be compensated for when the two modalities are used in a complementary way. High-resolution anatomic information produced by CT adds significant information to tissue characterization delivered by PET. In addition, fusion of high resolution MRI anatomic and functional information with PET will provide an extra dimension. When applying the integration of different imaging modalities, adequate anatomic alignment of both image sets is required. This permits convenient visualization of all information in one study.

The benefits of fusion imaging include: (Săftoiu and Vilmann, 2011 and Ghom *et al*., 2011)

- Improved lesion characterization thereby increasing the diagnostic accuracy. This is recognized as a beneficial diagnostic effect
- Direct comparison of the lesions using different imaging modalities
- Better identification of small recurrent tumours obscured by scar tissue at site of incipient radiation or postoperative necrosis
- Detection of large tumours in clinically inaccessible areas such as hypopharynx or maxilla
- Improved lesion localization may lead to better results in other successive diagnostic procedures (e.g., easier CT-guided biopsy)
- Moreprecise monitoring of interventional procedures
- Reduced radiation exposure

Hence, fusion imaging is an imaging modality with high diagnostic performance in assessment of head and neck cancer. Clinical applications of fusion imaging in the head and neck cancer include:

- Detection of unknown primary tumour (Ghom *et al*., 2011 and Subramaniam *et al*., 2010)
- Detection of synchronous second primaries (Subramaniam *et al*., 2010)
- Tumourstaging (Ghom *et al*., 2011 and Subramaniam *et al*., 2010)
- Diagnosis of distant metastases (Subramaniam *et al*., 2010)
- Detection of residual or recurrent disease (Subramaniam *et al*., 2010)

Emerging applications are:

- Precise delineation of the tumour volume for radiation therapyplanning (Ghom *et al*., 2011)
- Evaluating treatment and providing prognostic information (Ghom *et al*., 2011)
- Reference tool for surgical planning (Al-Ibraheem *et al*., 2009)

DISCUSSION

Staging of cancer

A literature survey on the use of 18F-FDG PET in head and neck cancer (HNC) compared to CT indicates that PET has a higher sensitivity (87% versus 62%) and specificity (89% versus 73%) for staging cancer. Addition of PET/CT to initial staging of patients with HNC has also been shown to have a measurable impact on the treatment selection. Table 1 shows various studies that compare the accuracy of FDG PET and PET/CT with CT and MRI for detection of lymph node metastases in head and neck squamous cell carcinoma (HNSCC) (Al-Ibraheem *et al*., 2009). Table 2 shows various studies evaluation the performance of FDG PET for the detection of distant metastases and synchronous 2^{nd} tumour in HNC. These studies showed that PET detected distant metastases or 2nd primaries in up to 15.6% of the patients. The true positive findings were 82%. Moreover, PET showed a better accuracy once it was compared to conventional imaging as demonstrated by Ng *et al*., 2009; Chua *et al*., 2009 and Liu *et al*., 2007.

A study was conducted by Loeffelbein *et al*. (2014) to assess the diagnostic value of retrospective PET-MRI fusion and to compare the results with side-by-side analysis and single modality use of PET and of MRI alone for locoregional tumour and nodal staging of head-and-neck cancer. The overall sensitivity/specificity for tumour staging for MRI, PET, side-by-side analysis and retrospective PET-MRI fusion was 79%/66%, 82%/100%, 86%/100% and 89%/100%, respectively. The overall sensitivity/specificity for nodal staging on a patient basis for MRI, PET, side-by-side analysis and PET-MRI fusion was 94%/64%, 94%/91%, 94%/82% and 94%/82%, respectively. MRI, PET, side-by-side analysis and retrospective image fusion were associated with correct diagnosis/over-staging/under-staging of N-staging in 70.4%/18.5%/11.1%, 81.5%/7.4%/11.1%, 81.5%/11.1%/7.4% and 81.5%/11.1%/7.4%, respectively (Feichtinger *et al.,* 2007).

Unknown primary

Cervical lymph node metastases from an unknown primary tumour account for approximately 1-2% of newly diagnosed head and neck cancers. In 5% to 80%, depending on the patient selection, the primary tumour are not be identified by physical examination and conventional imaging, including CT and/or MRI. Treatment of these patients often includes extensive fields of irradiation to include the entire pharyngeal mucosa, larynx, and bilateral neck. The wide-field irradiation reduces the risk of tumour recurrence. However, it also causes significant morbidity, particularly in terms of xerostomia. Therefore, the accurate identification of occult primary sites is important because the therapy can then be focused to the known site of origin, decreasing treatment-related morbidity, and improving therapeutic efficacy. Table 3 shows studies evaluating performance of FDG PET or PET/CT in detecting carcinoma of unknown primary in patients who presented with cervical lymph node metastases and negative or inconclusive standard workup. For this group, 18F-FDG PET and PET/CT detected the primary tumour in 51 of 180 patients (28%) (Al-Ibraheem *et al*., 2009).

Table 1.

Author year	Number of patients	Tumour Subtypes	Results	Notes
Beak *et al.* (2009)	15	Periorbital	PET/CT accuracy (98%) > CT 84%	CT: 16 slice PET modified Tx in 39%
Roh *et al.* (2007)	167	HNSCC	PET or PET/CT accuracy (92%-93%) > CT/MR 85%-86%	PET/CT significantly better for detection of primary tumour
Gordin *et al.* (2007)	35	Nasopharyngeal	PET/CT accuracy 91% > PET 80% > CT 60%	Retrospective PET/CT modified Tx in 57%
Kim *et al.* (2007)	32	Oropharyngeal	PET sensitivity 21% higher than CT/MR (p< .05)	PET/CT significantly better for detection of primary tumour
Dammann *et al.* (2005)	79	Oral cavity and oropharynx	PET accuracy 96% > MRI 94% > CT 92%	Nonhybrid PET/CT used
Ng *et al.* (2006)	124	Oral cavity SCC	PET accuracy 98.4% > CT/MR 87.1%	Prospective

Table 2.

Author year	Number of patients	Positive PET	True positive (distant mets + 2nd primary)	False positive	Notes
Ng *et al.*(2009)	111	16	13/16	3/16	CT/MR detect 4/16
Chua *et al.* (2009)	68	6	5/6	1/6	CT + BS detect 4/6
Liu *et al.* (2007)	300	61	50/61	11/61	
Yen *et al.* (2005)	118	32	24/32	8/32	
Goerres *et al.* (2003)	34	8	7/8	1/8	PET modified Treatment in 15%
Sigg *et al.* (2003)	58	8	7/8	1/8	PET modified Treatment in 5%
Schwartz *et al.* (2003)	33	7	7/7	0/7	
Total	722	138	113/138	25/138	

Table 3.

Author year	Number of patients	All positive	True positive	False positive	Percent detected by PET
Padovani *et al.* (2009)	13	9	7	2	54%
Silva *et al.* (2007)	25	9	3	6	12%
Fakhry *et al.* (2006)	20	10	7	3	35%
Wong and Saunders (2003)	17	8	5	3	29%
Fogarty *et al.* (2003)	21	6	1	5	5%
Johansen *et al.* (2002)	42	20	10	10	24%
Kresnik *et al.* (2001)	15	12	11	1	73%
Jungehulsing *et al.*(2000)	27	7	7	0	26%
Total	180	81	51	30	28%

Table 4.

Authors year	*Number of patients*	*Sensitivity*	*Specificity*	*Accuracy*	*Notes*
Abgral *et al.* (2009)	91	100%	85%	90%	FDG PET/CT
Wang *et al.* (2009)	44	100%	98%	98%	Prospective PET performance > CT
Cermik *et al.* (2007)	50	83%	93%		
Alvarez perez *et al.* (2007)	60	98%	90%		Prospective
Salaun *et al.* (2007)	30	100%	95%	97%	
Goerres *et al.* (2004)	26	91%	93%		Prospective
Kubota *et al.* (2004)	36	90%	78%		Prospective Accuracy significantly higher than CT/MR

Table 5.

Author year	Number of patients	Study type	Results	Notes
Soto *et al.* (2008)	61 (9 LRF)	Retrospective	8/9 LRF within BTV-PET	
Rothschild *et al.* (2007)	45	Case-control analysis	PET/CT with IMRT improved cure rates	Advanced pharyngeal carcinoma
Wang *et al.* (2006)	28	Prospective	PET/CT-based GTV significantly different from CT scans alone in 50% of cases	PET/CT upgraded T and N stage in 18 cases
Breen *et al.* (2007)	10		No significant differences in the GTVs between PET/CT and CT alone	CT volumes were larger than PET/CT
El-Bassiouni *et al.* (2007)	25		PET/CT based volume significantly smaller than CT	
Koshy *et al.* (2005)	36	Retrospective	TNM changed in 36%, RT volume and dose changed in 14%	
Heron *et al.* (2004)	21	Prospective	PET/CT improves delineation of normal tissues from tumour areas	PET/CT improves staging
Ciernik *et al.* (2003)	12 HNC of 39	Retrospective	PET/CT changed GTV in 50% compared to CT	
Nishioka *et al.* (2002)	21		PET improves GTV, normal tissue sparing	P*ET al*one

(IMRT) intensity-modulated radiation therapy, (GTV) gross target volume, (LRF) locoregional failure

Recurrence

18F-FDG PET and PET/CT have a high sensitivity and moderate specificity for detecting recurrent disease at the primary tumour site, regional lymph node metastases and distant metastases. Several studies on the utility of PET or 18F-FDG PET/CT for the detection of recurrence are summarized in Table 4 (Al-Ibraheem *et al*., 2009).

Radiation treatment planning

New high-precision radiotherapy (RT) techniques, such as intensity-modulated radiation therapy (IMRT), 3-dimensional conformal radiotherapy (3D-CRT), and proton beam therapy allow conformal treatment of tumour and to avoid unacceptable damage to normal tissues leading to possible improvement of tumour control and decrease of treatment-related toxicity. These techniques depend on imaging modalities allowing accurate tumour volume delineation and response assessment during treatment. The potential application of 18F-FDG PET/CT forintensity modulated radiation therapy (IMRT) planning is an area of major interest. Table 5 summarizes recent studies on the use of 18F-FDG PET and PET/CT in radiotherapy planning (Al-Ibraheem *et al*., 2009).

Conclusion

The additional information provided by image fusion significantly improves diagnostic accuracy and localization of malignant lesions and is superior to conventional anatomical and functional imaging techniques especially in areas of complex anatomy. There is improved utilization of patient data, thereby improving patient care. Hybrid technology has the potential to revolutionize diagnostics and has emerged as a promising diagnostic tool. Their clinical value for HNC has not been fully defined yet and must be analysed systematically. Further detailed clinical studies and imaging are required to substantiate their performance in oncologic imaging.

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