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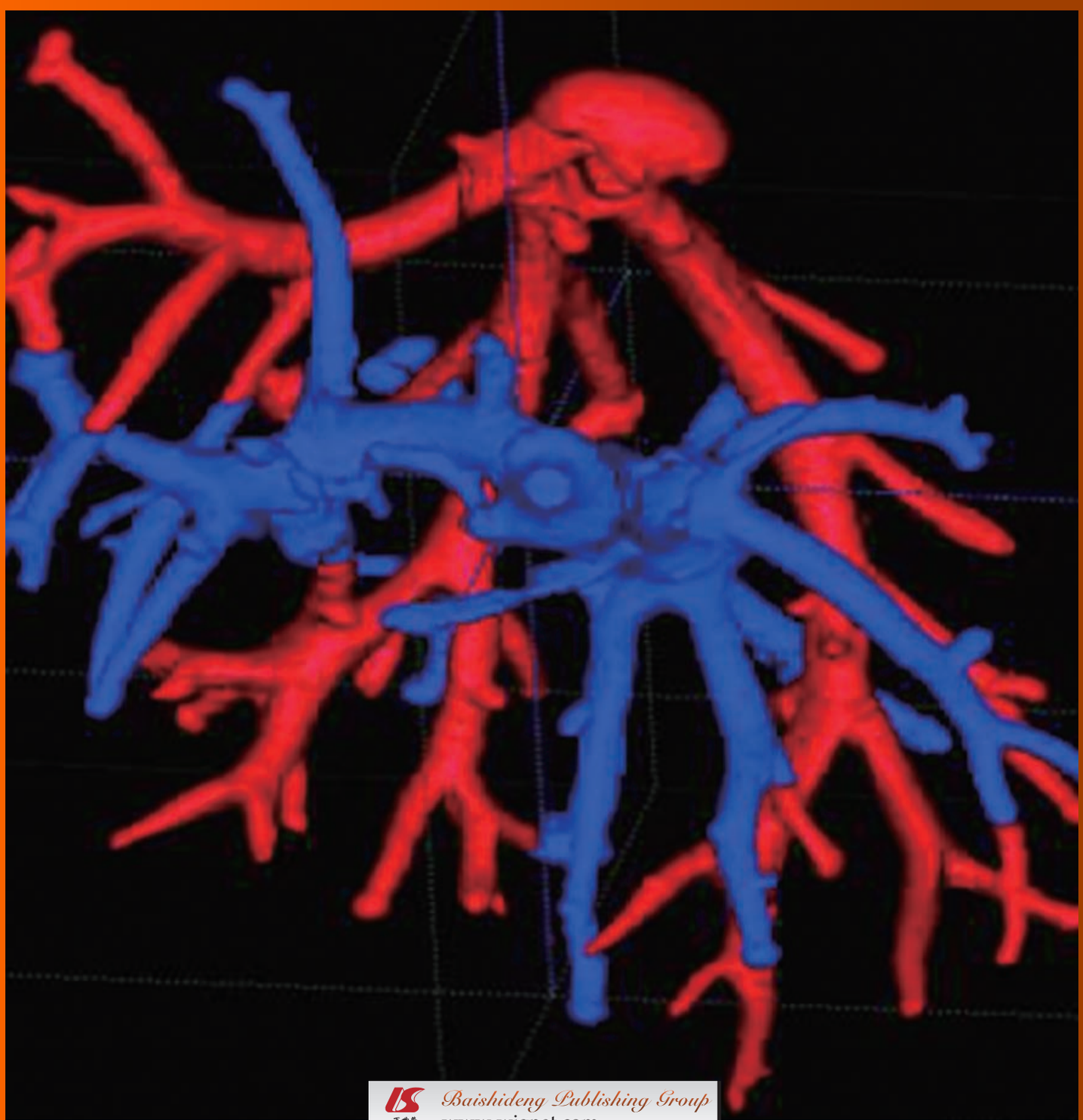

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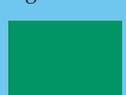

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BRIEF ARTICLE

Dynamic contrast-enhanced MR imaging findings of bone metastasis in patients with prostate cancer

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Abstract

AIM: To evaluate the dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) findings of bone metastasis in prostate cancer patients.

METHODS: Sixteen men with a diagnosis of metastatic prostate cancer to bones were examined with DCE-MRI at 1.5 Tesla. The mean contrast agent concentration *vs* time curves for bone metastasis and normal bone were calculated and K^{trans} and *ve* values were estimated and compared.

RESULTS: An early significant enhancement (wash-out: $n = 6$, plateau: $n = 8$ and persistent: $n = 2$) was detected in all bone metastases ($n = 16$). Bone metastasis from prostate cancer showed significant enhancement and high K^{trans} and *ve* values compared to normal bone which does not enhance in the elderly population. The mean K^{trans} was 0.101/min and 0.0051/min ($P < 0.001$), the mean *ve* was 0.141 and 0.0038 ($P < 0.001$), for bone metastases and normal bone, respectively.

CONCLUSION: DCE-MRI and its quantitative perfusion parameters may have a role in improving the detection of skeletal metastasis in prostate cancer patients.

Key words: Prostate; Cancer; Bone; Metastasis; Dynamic contrast-enhanced MR imaging

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INTRODUCTION

Prostate cancer is the most commonly diagnosed non-skin cancer in men in the United States. As per the latest estimates by American Cancer Society in 2009 about 192 280 new cases of prostate cancer will be diagnosed and 27 360 men will die of the disease[1]. It is known that most patients with locally advanced prostate cancer will also have probable occult metastases at diagnosis. The

most important determinant of potentially curative therapies and of appropriate palliative management for prostate cancer during early staging is accurate assessment of the extent of the metastatic process[2].

The most frequent sites of distant metastases of prostate cancer are bones and typically vertebra[3,4]. The diagnosis, location, burden and monitoring of metastatic bone involvement plays a crucial role in patient management and prognosis. Imaging bone disease in prostate carcinoma generally involves a cascade of studies starting with bone scintigraphy followed by magnetic resonance imaging (MRI), computed tomography (CT) or positron emission tomography/CT. Conventional MRI is sensitive to early changes in bone marrow that precede the osteoblastic response in the bone matrix. However, detection rates for bone metastases using MR range between 7% and 38% and its use is still limited[4,5]. Recently, newer MRI methods such as diffusion-weighted imaging and dynamic contrast-enhanced MRI (DCE-MRI) are also addressing the lack of quantitative assesment of skeletal metastases.

DCE-MRI has been increasingly used as an additional technique to characterize various bone lesions, grading disease, planning and guiding biopsy and monitoring response to radio- and/or chemotherapy and detecting early local recurrence[6,7]. It provides a powerful tool for assessing angiogenesis and measuring properties of tissue vasculature, including blood volume and vascular permeability in tumor tissues. In this study, we aimed to evaluate DCE-MRI findings of bone metastasis in patients with prostate cancer.

MATERIALS AND METHODS

Subjects

The study group consisted of 16 men (age range: 49-79 years; median age: 65 years) with histologically proven adenocarcinoma of the prostate with skeletal metastasis. The study was approved by the institutional review board and informed consent was obtained. Each patient underwent clinical CT scan and bone scan prior to this study and the sites of bone metastasis was determined based on CT and bone scan findings. As part of the research protocol, bone metastases in regions with minimal motion artifact were scanned by research DCE-MRI protocol. In one patient, the scanned bone metastasis was in the shoulder and in 15 patients it was in the pelvic region. None of the metastatic lesions were treated before MRI.

MR imaging

MR images were acquired on a 1.5T GE MRI scanner (SIGNA™, GE Medical Systems, Waukesha, WI, USA). Following a scout scan to localize the lesions, T1-weighted (T1W) images were acquired at 2 s temporal resolution for 1 min before and 6 min after the injection of 0.1 mmoL/kg gadodiamide (Omniscan, GE Healthcare, Chalfont St. Giles, UK). The contrast agent and 20 mL saline flush was injected with an automated injector (Medrad, Indianola, PA, USA) at the rate of 2 mL/s in an antecubital vein. A 2D fast spoiled gradient-echo pulse sequence was used with TR/TE = 7.8/1.7 ms, flip angle 60°, matrix size 256 × 128, field of view 30-35 cm, 2 slices, slice thickness 8 mm, slice spacing 1 mm. The axial slices in which the lesion was in its largest dimension were selected.

Data analysis

For each subject, an experienced radiologist placed the region of interest (ROI) on the bone metastasis and normal bone in the DCE-MRI after reviewing the clinical CT and bone scan images. Any vessels at the lesion margin were carefully excluded from the bone metastasis ROI. For normal bone, muscle and bone metastasis the mean ROI size was 3.1 cm^2 (median 3.2 cm^2, range 1.1-5.7 cm^2), 16.4 cm^2 (median 13.9 cm^2, range 6.6-33.8 cm^2) and 14.3 cm^2 (median 10.0 cm^2, range 5.0-33.7 cm^2), respectively.

The enhancement patterns of bone metastasis and normal bone were analyzed regarding presence of early enhancement, washout, plateau and persistence of enhancement. The contrast agent concentration was calculated as previously described[8]. Contrast agent arterial input function (AIF), which is the contrast agent concentration in the blood plasma, was estimated with a multiple reference tissue method using tumor voxels and muscle as described by Yang *et al*[8,9]. The mean contrast agent concentration *vs* time curve [$C_t(t)$] was calculated for each bone metastasis ROI and normal bone ROI. Using the estimated individual AIF, contrast agent transfer rate between blood and tissue (K^{trans}) and the extra-vascular extra-cellular fractional volume (v_e), were then estimated under the Tofts model[10].

Statistical analysis

Two-tailed paired Student's *t*-test was used to test the difference in K^{trans} and v_e between bone metastasis and normal bone. Statistical analysis was performed using SPSS Software System version 15.0 (SPSS Inc., USA).

RESULTS

All of the bone metastases showed early significant enhancement (wash-out: 6, plateau: 8 and persistent: 2) (Figures 1 and 2). On the other hand, normal bone demonstrated negligible enhancement in 15 patients. There was minimal enhancement of normal bone in only one patient.

For the 16 bone metastases, the mean K^{trans} was 0.101/min (range 0.034-0.290/min, median 0.071/min) and mean v_e was 0.141/min (range 0.080-0.234/min, median 0.141/min). For the 16 normal bones, the mean K^{trans} was 0.0051/min (range 0.0-0.080/min, median 0.0/min), ($P < 0.001$). The mean v_e of normal bone was 0.0038 (range from 0.0-0.048, median 0.0), also significantly lower than that in bone metastases ($P < 0.001$). Based on quantitative analysis, normal bones showed slightly negative enhancement or very weak enhancement. In one 69-year-old patient, the normal bone showed a moderate enhancement with a K^{trans} value of 0.080/min and a small v_e value of 0.048. Figure 2 shows the $C_t(t)$ curve of bone metastasis and normal bone, as well as the pre-contrast image, the average early subtrac-

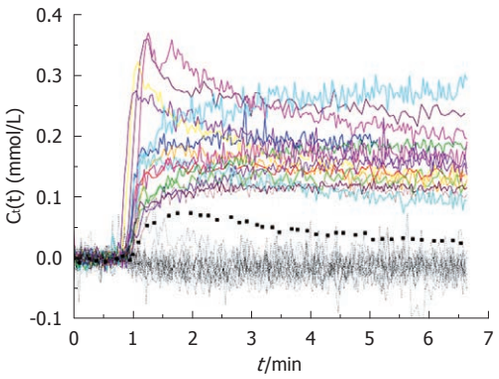

Figure 1 Contrast agent concentration *vs* time curves in bone metastases (colored solid lines) and normal bones (black dotted lines). The curve from the only enhancing normal bone was highlighted by thick black dotted line. The enhancement of the normal bone was much less than the metastatic lesions.

tion image, and the average late subtraction image in two representative patients.

DISCUSSION

Approximately 70% of patients with advanced prostate cancer develop skeletal metastasis[11,12]. MRI appearance of normal bone marrow reflects variable amounts of its physiological components, primarily fat cells and hemopoietic cells. Although bone marrow that contains mostly fat cells can be depicted by conventional MRI techniques (including T1W, T2W and fat saturated imaging), these techniques are often not able to differentiate tumor infiltration, fibrosis and normal red bone marrow. Additionally, for a malignant marrow lesion to be visible on conventional MRI scan, it must replace sufficient normal marrow cells so that it can cause alterations in T1 and T2 relaxation values. However, as the perfusion of normal bone marrow is strongly influenced by the age of the patient and fat content of the marrow, the contrast enhancement of normal bone marrow decreases markedly with increasing age and conversion to fat, while the tumor cells demonstrate enhancement[7,13,14]. Our study group consisted of patients with an age range of 49-79 years and no enhancement was detected in normal bones in the vast majority (15/16) of the patients. As the metastatic tumor has increased enhancement levels, the tumor foci can be easily detected in the background of non-enhancing bone marrow on contrast-enhanced MR images. Therefore, contrast enhanced MRI may be an important tool for detection of bone metastasis for the elderly population of prostate cancer patients.

There have been many studies searching the microvascularization of bone marrow with different DCE-MRI techniques in which qualitative, semiquantitative and quantitative methods have been reported to depict tissue perfusion parameters[15-18]. Tokuda et al analyzed 34 patients with benign and malignant vertebral lesions in which peak enhancement, steepest slope and slope value were calculated from the time intensity curve (TIC)[19]. They showed that the steepest slopes of metastatic lesions were significantly higher than those of benign lesions and no characteristic distribution of the TIC pattern was found to help in differentiation of benign and metastatic lesions. Chen *et al* investigated the peak contrast enhancement percentage, enhancement slope and the TIC patterns of the first pass of contrast into vertebral lesions. They found that metastatic vertebral lesions had a higher peak enhancement percentage and steeper enhancement slope than lesions of benign etiology[6]. They also concluded that type D (rapid wash in and wash out) and E (rapid wash in followed by a second slow-rising phase) curves are valuable in differentiating benign and malignant vertebral lesions. Both of these studies evaluated angiogenesis and perfusion of bone metastasis using semi-quantitative parameters. Recently, a few studies have looked into more advanced quantitative analysis methods to potentially increase accuracy and reproducibility of DCE-MRI. Baurle *et al* evaluated the amplitude and exchange rate constant (Kep) of the enhancement of bone metastasis in an animal model of breast cancer[20]. They found that amplitude decreased significantly prior to changes in osteolytic lesion size following treatment of bone metastasis. On the other hand, there was no significant change in Kep between the treated group and control group.

In our study, by using quantitative parameters obtained from high temporal resolution DCE-MRI data, we demonstrated that in elderly prostate cancer patients, bone metastasis showed much faster and higher enhancement than normal appearing bones. The difference in their contrast concentration levels lasted for the entire 5.5 min of contrast enhancement duration. These results suggests that it may be possible to detect bone metastasis at a delayed contrast enhanced phase after 3 min of contrast administration instead of imaging the patients continuously at high temporal resolution for several minutes. However, quantitative analysis of DCE-MRI data can provide quantitative information about the bone metastasis which cannot be obtained by bone scan and CT. Further studies are needed to investigate whether DCE-MRI derived perfusion parameters may be used as biomarkers in evaluation of treatment response of bone metastasis in patients with prostate cancer.

The limitation of our study is that the quantitative parameters obtained from metastatic lesions were compared with the findings of normal bone in the same patient rather than benign bone lesions. The parameters of metastatic bone lesions other than prostate were also not compared. Moulopoulos *et al*[21] evaluated cancer patients with metastasis to bone marrow including lymphoma, chronic lymphocytic leukemia, carcinoma of the cervix, breast, lung and bladder. They compared the wash-in and wash-out rates, time to peak, and time to maximum slope values of control group with no history of malignancy and reported a significant difference for all values.

In conclusion, bone metastasis from prostate cancer demonstrates significant enhancement leading to high K^{trans} and v_e in contradiction to normal bone which does not enhance in the elderly population. DCE-MRI and its

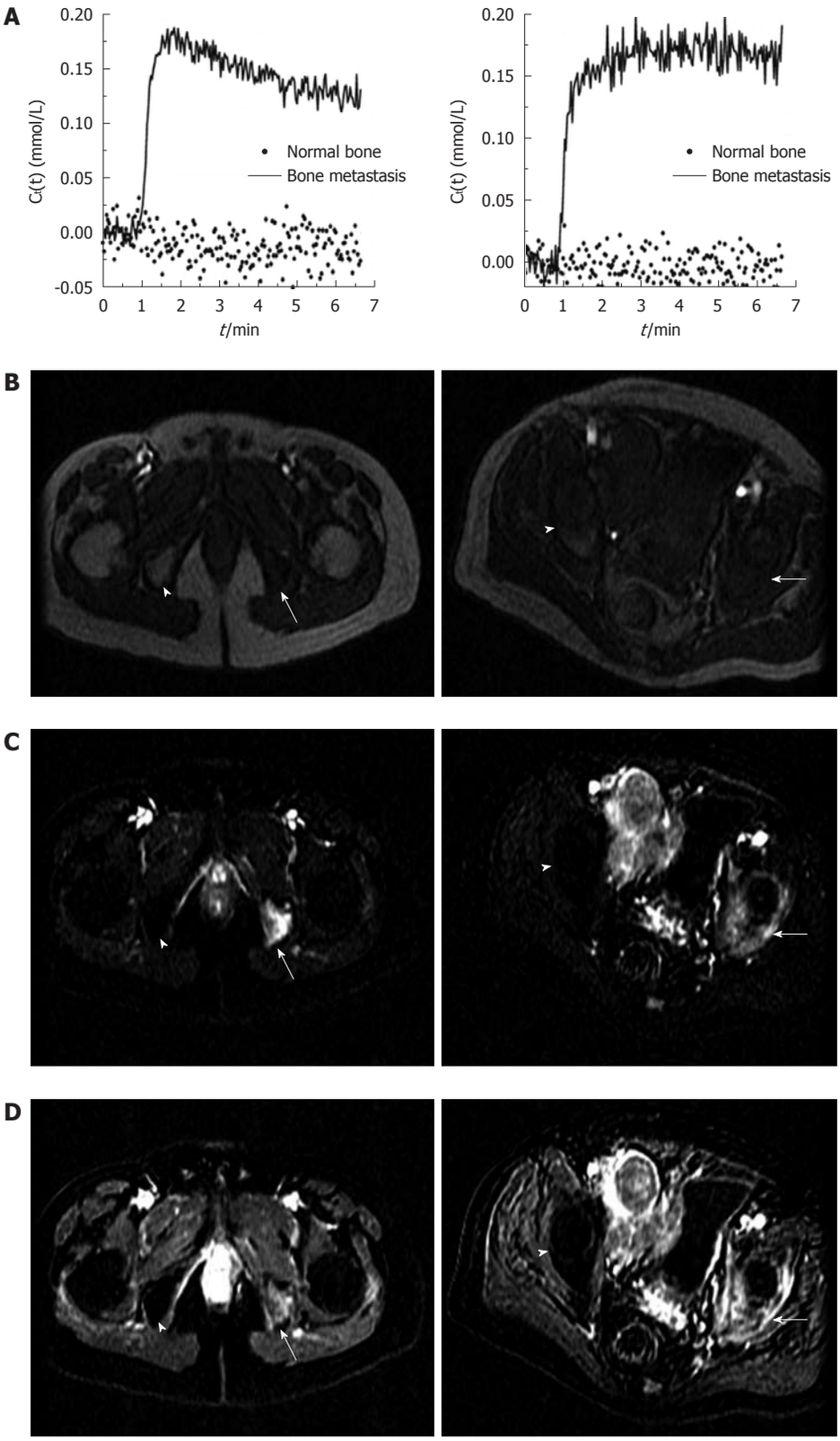

Figure 2 Pelvic bone metastasis on the left side in a patient with prostate cancer compared with normal pelvic bones on the right side. A: Contrast agent concentration *vs* time curve of bone metastasis region of interest (ROI) and normal bone ROI; B: Pre-contrast image (arrow: bone metastasis, arrowhead: normal bone); C: The average subtraction image for the first minute after bolus arrival; D: The average subtraction image for the last 1 min in two representative patients (arrow: bone metastasis, arrowhead: normal bone).

quantitative analysis may have a role in improving the detection of bone metastasis from prostate cancer.

COMMENTS

Background

Prostate cancer is a major health problem and a major cause of death in men. It is crucial to determine the assessment of the metastatic process of prostate cancer for designing a proper treatment. The most frequent sites of distant metastases of prostate cancer are bones. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and its quantitative analysis may contribute to improve the detection of bone metastasis from prostate cancer.

Research frontiers

DCE-MRI has been increasingly used as an additional technique to characterize various bone lesions. It provides a powerful tool for assessing the tissue vasculature in tumor tissues. In this study, the authors demonstrate the contribution of DCE-MRI for detection of bone metastasis in patients with prostate cancer.

Innovations and breakthroughs

In recent studies searching the microvascularization of bone marrow, mostly qualitative and semiquantitative DCE-MRI techniques were used. This study investigated quantitative parameters obtained from high temporal resolution DCE-MRI data of bone metastasis from prostate cancer. Furthermore, our study demonstrated that bone metastasis from prostate cancer shows significant enhancement leading to high K^{trans} and v_e in contradiction to normal bone which does not enhance in the elderly population.

Applications

Quantitative measurements of DCE-MRI data may improve the diagnosis of bone metastasis by providing quantitative analysis which cannot be obtained by bone scan and CT. Therefore, this study may represent a future perspective for DCE-MRI derived perfusion parameters, which may be used as biomarkers in evaluation of treatment response of bone metastasis in patients with prostate cancer.

Terminology

DCE-MRI provides a powerful tool for measuring alterations in the microvascular environments of the tissue. K^{trans} and v_e, are quantitative parameters of DCE-MRI and they are expected to be increased in bone metastasis from prostate cancer, in contrast to normal bone in the elderly population.

Peer review

Although this study did not perform the reproducibility of quantitative perfusion parameters in bone metastasis from prostate cancer, the topic of this article may draw the readers' attention. This study may be an initial step to assess the roles of quantitative perfusion parameters in monitoring or predicting therapeutic responses for advanced prostate cancer patients in the future studies. Generally this article is well-written.

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CASE REPORT

Lipoma of the pancreas, a case report and a review of the literature

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Author contributions: Lee SY designed, carried out the extraction of the patient's clinical data, performed critical appraisal of the literature and wrote the manuscript; Thng CH selected the radiological images, assisted in the expert review of the radiological aspects of the case report and assisted in writing the manuscript; Chow PKH supervised and critically reviewed the manuscript; Lee SY and Chow PKH were both directly involved in the care of the patient; all authors contributed significantly to this work, read and approved the final manuscript.
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Abstract

Lipomas of the pancreas are very rare. There are fewer than 25 reported cases of lipoma originating from the pancreas. We present a case of pancreatic lipoma in a 61-year-old woman with magnetic resonance imaging findings and confirmatory histological findings. We discuss and highlight the radiological features distinguishing a pancreatic lipoma from other fatty lesions of the pancreas and pancreatic liposarcoma and provide a brief review of the literature.

Key words: Lipoma; Liposarcoma; Pancreas; Fat-containing pancreatic tumors

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INTRODUCTION

Pancreatic tumors arise from cells of mesenchymal or epithelial origin, or from non-ductal structures and fat. Epithelial tumors constitute the largest group including adenocarcinoma which account for 85% of all pancreatic tumors. Non-ductal tumors account for 5%-15%, and mesenchymal tumors account for about 1%[1]. Among these, fat-originating tumors such as lipoma and liposarcomas are the rarest.

CASE REPORT

A 61-year-old woman with a past medical history of dyslipidemia and cholelithiaisis was admitted to our institution for right hypochondrium pain and epigastric discomfort and vomiting of 2 wk duration. Her liver function tests revealed mild transaminitis with alanine transaminase 246 U/L, aspartate transaminase 308 U/L, raised alkaline phosphatase (ALP) 188 U/L and γ-glutamyl transferase (GGT) 408 U/L. The tumor marker carbohydrate antigen 19-9 was slightly raised, 52.2 U/mL (reference range 3-50 U/mL). Physical examination was normal. Ultrasonography revealed multiple subcentimetre gallstones; the pancreas was noted not to be well visualized due to overlying bowel gas. She was treated symptomatically for biliary colic and was discharged well with a view for an elective laparoscopic cholecystectomy. In view of her persistent raised ALP and GGT, a magnetic resonance chol-

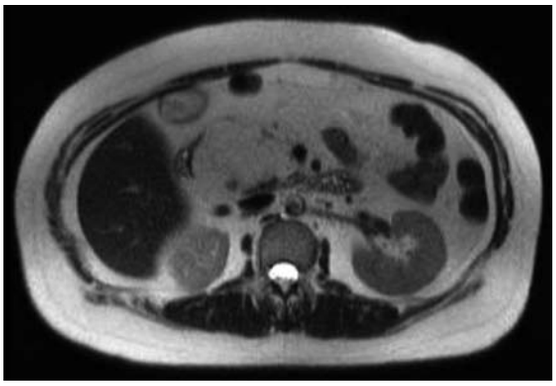

Figure 1 T2 magnetic resonance image. This cross sectional image reveals a 6.8 cm x 4.4 cm fat containing lesion arising from the pancreatic head, scalloping the pancreatic head and displacing the duodenum.

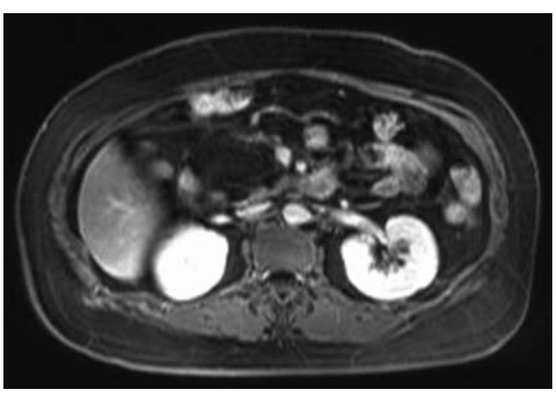

Figure 2 T1 weighted magnetic resonance imaging phase. This cross sectional image reveals a homogenous fatty containing lesion in the head of pancreas.

angiopancreaticography was performed during follow-up. It revealed a 6.8 cm × 4.4 cm fat containing lesion arising from the pancreatic head, scalloping the pancreatic head and displacing the duodenum (Figures 1 and 2).

Because of its size, liposarcoma could not be excluded. A Whipple's procedure was performed and the final histology of the lesion was a pancreatic lipoma. Post-operative recovery was uneventful and she was discharged in a healthy condition.

DISCUSSION

Lipomas are made up of mature adipose cells within a thin collagen capsule. They can be found almost anywhere in the body where there is adipose tissue. When found intra-abdominally, they frequently arise from the gastrointestinal tract, although they can be found in other rare locations such as the pancreas. In the literature there are less than 25 cases of pancreatic lipoma[2] and 4 cases of pancreatic liposarcoma reported to date. The first reported case was described by Bigard *et al*[3] in 1989 as a hypoechoic mass in the head of the pancreas and this was histologically confirmed as a lipoma. Several imaging modalities were used in the reported cases for diagnosis. Katz *et al*[4] presented 4 cases of pancreatic lipoma diagnosed on computed tomography (CT), showing a homogenous lesion composing of fat. Legmann *et al*[5] defined the CT findings of a pancreatic lipoma. CT findings for a pancreatic lipoma include homogenous distribution of fat density with no central or peripheral contrast enhancement, Housefield units of -80 to -120 and a sharp demarcation with no evidence of intra- and extra-pancreatic adjacent structures infiltration. Some of these characteristics were used as a definition by Ozelm *et al*[2]. Ultrasonography was used in a series by Itai *et al*[6]. Elliott *et al*[7] reported a case of pancreatic liposarcoma with plain abdominal X-rays. Di Matteo *et al*[8] reported a case of pancreatic lipoma that was diagnosed on endoscopic ultrasonography.

Besides lipoma of the pancreas, fatty lesions in the pancreas include focal fatty infiltration of the pancreas, teratoma and liposarcoma. Liposarcoma is itself a heterogeneous group. Classification of liposarcoma into subtypes is based on morphologic features and cytogenetic aberrations; namely, the 5 subtypes are well-differentiated, de-differentiated, myxoid, round cell and pleomorphic[9]. Magnetic resonance imaging (MRI) has been used to characterize the different groups of liposarcomas in the retroperitoneum. Well-differentiated liposarcoma presents as high signal intensity on T1-weighted (T1W) images, intermediate signal intensity on T2-weighted (T2W) images and drop-out signal intensity on fat-suppressed MR images. De-differentiated liposarcoma has clear demarcations between fat and non-adipose solid tissues and reveals small amounts of fatty components. Myxoid liposarcoma has a low signal intensity on T1W image and high signal intensity on T2W image. Round-cell liposarcoma and pleomorphic liposarcoma have soft tissue tumor signal intensity without the characteristic fat signal. This suggests MRI as the ideal imaging modality for retroperitoneal liposarcomas as it can demonstrate its margins and internal components[9]. In a review and meta-analysis of the role of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in soft tissue sarcomas, the results indicate that FDG-PET can discriminate between sarcomas and benign tumors and low and high grade sarcomas based on the mean standard uptake value[10].

It has been suggested that both focal fatty infiltrations and lipomas can be managed conservatively in asymptomatic and incidental cases. A presumptive diagnosis of lipoma can be made if the lesion is purely fat containing no solid areas and is small (< 3 cm) in size. In the literature, there are no definite diagnostic criteria based on size for distinguishing a lipoma from a liposarcoma in the retroperitoneum. In fact, the tumor burden (the sum of the maximum diameter of the primary tumors) has been reported in a series to be as small as 5 cm. For liposarcomas, a large (> 10 cm) size, arising from a retroperitoneal site, as well as an involved resection margin, are reported as adverse prognostic factors[11].

Most investigators believe that histology is not absolutely necessary to confirm the diagnosis of pancreatic lipoma because radiologic features are almost diagnostic. However, a well-differentiated lipogenic liposarcoma may mimic a benign lesion because of homogeneity of fat

and its sharply defined margins on imaging.

Retroperitoneal liposarcomas are rare and pancreatic liposarcomas are even more uncommon with eventual metastases reported in 30%-60% of cases[12]. Only 4 cases of pancreatic liposarcoma have been reported, with minimal radiologic data[1,3]. The reported pancreatic liposarcomas range from 9 to 16 cm in largest diameter and diagnosis is retrospective in nature and is not achieved based on imaging alone[13,14]. A retrospective review of our departmental records identified 21 patients with primary retroperitoneal liposarcoma treated between July 1990 and June 2005. There have been no liposarcomas related to the pancreas in our institution to date[14].

In our case, the lesion is large and it is difficult to rule out the possibility of liposarcoma. The patient also has pain associated with symptoms of gastric outlet obstruction from compression of the duodenum and has a persistently abnormal liver function test. Hence a decision was made to perform a Whipple's procedure to excise the tumor.

In summary, lipomas of the pancreas are very rare. The exact radiological diagnosis to differentiate it from other fat-containing lesions can be difficult. Several radiological modalities have been used, of which MRI proves to be the most useful[15]. An asymptomatic or incidental lesion can be managed conservatively and monitored with serial imaging. However, if it is compressing on vital structures e.g. ampulla of vater or duodenum, causing symptoms or if there are any suggestions of malignant change e.g. large size, rapid growth or radiologically heterogeneous, surgery can be offered as an option for treatment and histopathological confirmation.

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Theranostic applications: Non-ionizing cellular and molecular imaging through innovative nanosystems for early diagnosis and therapy

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Abstract

Modern medicine is expanding the possibilities of receiving "personalized" diagnosis and therapies, providing minimal invasiveness, technological solutions based on non-ionizing radiation, early detection of pathologies with the main objectives of being operator independent and with low cost to society. Our research activities aim to strongly contribute to these trends by improving the capabilities of current diagnostic imaging systems, which are of key importance in possibly providing both optimal diagnosis and therapies to patients. In medical diagnostics, cellular imaging aims to develop new methods and technologies for the detection of specific metabolic processes in living organisms, in order to accurately identify and discriminate normal from pathological tissues. In fact, most diseases have a "molecular basis" that detected through these new diagnostic methodologies can provide enormous benefits to medicine. Nowadays, this possibility is mainly related to the use of Positron Emission Tomography, with an exposure to ionizing radiation for patients and operators and with extremely high medical diagnostics costs. The future possible development of non-ionizing cellular imaging based on techniques such as Nuclear Magnetic Resonance or Ultrasound, would represent an important step towards modern and personalized therapies. During the last decade, the field of nanotechnology has made important progress and a wide range of organic and inorganic nanomaterials are now available with an incredible number of further combinations with other compounds for cellular targeting. The availability of these new advanced nanosystems allows new scenarios in diagnostic methodologies which are potentially capable of providing morphological and functional information together with metabolic and cellular indications.

Key words: Intelligent nanosystems for cellular targeting; Magnetic resonance and ultrasound; Molecular imaging; Non-ionizing diagnostic techniques; Personalized medicine in the oncological and vascular field

Peer reviewer: Frederik L Giesel, MD, PhD, MBA, National German Cancer Research Center (dkfz), Department of Radiology E010, 69120 Heidelberg, Germany

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INTRODUCTION AND EDUCATIONAL EXPERIENCE

Sergio Casciaro (Figure 1) was born in Lecce, Italy in 1971. He received his Laurea degree in Nuclear Engineering at Turin Polytechnic Engineering School (Politecnico di Torino) and his PhD in Bioengineering in 2003 at the University of Pisa.

From 1996, he was a research engineer at CERN - European Centre for Nuclear Research, Geneva, Switzerland, working on the design and tests of the Large Hadron Collider for high energy physics studies. Then, in 1998 he moved to EPFL - Swiss Federal Institute of Technology, Lausanne, Switzerland for a research program on thermo-fluid dynamic experiments working on an ASHRAE research investigation. Then he went to ISBEM - Istituto Scientifico Biomedico Euro Mediterraneo, Brindisi, Italy for advanced studies in the biomedical field with a special focus on image and signal processing of magnetic resonance imaging (MRI) and contrast-enhanced ultrasound (US) data. In 2000 and 2001 he was a visiting scientist at NIH - National Institute of Health, Bethesda, USA working with P.A. Bandettini in the functional imaging unit for advanced functional and morphological investigations of the brain. From 2002 he has been a research scientist at the National Council of Research, Institute of Clinical Physiology and leader of the Biomedical Engineering Science and Technology Division and director of the Nanoimaging Ultrasound LAB for non-ionizing cellular and molecular imaging using innovative nanosystems for diagnosis and therapy. He is and has been in charge of several national and European research projects. He is on the Expert Evaluator Panel of the European Commission for the 7th Framework Program (Health, NMP, *etc.*). He is a reviewer for the following international journals: *Investigative Radiology*, *European Radiology*, *Radiology*, *Biomaterials*, *NeuroImage*, *Magnetic Resonance Imaging*, *IEEE TMI* and others. He is an editorial board member of the *World Journal of Radiology*.

Dr. Casciaro is a member and chair of the scientific committee of several scientific associations (NESA Academy; ARISER Network; ICAR; MIMOS; CARS; LSMU-International Medical University, Berlin, Germany). He has been an invited lecturer at the Bioengineering Course at Lecce University and Invited Professor at 6 national and international master courses on advanced medical imaging methods and techniques. He is Editor in Chief of 3 international books and co-author of about 20 book chapters. He is the author of more than 70 scientific articles in peer-reviewed journals and international conference proceedings. He is the main inventor of 5 national and international patents. He has been appointed scientific director of the ARISER Annual Conference for 5 years. He received several awards and prizes as Young Investigator and in 2010 he was awarded the prestigious National Prize for Innovation by the PNICube National Association as well as the "Prize of Prize for Research" by the President of the Italian Republic at the Quirinale Palace in Rome, June 2011.

ACADEMIC STRATEGY AND GOALS

Sergio Casciaro has 15 years experience in multidisciplinary research at international level, as documented in detail in the next paragraphs. In particular, during the last decade, his research activities have been related to the development of novel methodologies for biomedical image and signal processing, and through the introduction of new contrast media, towards innovative and minimally invasive diagnoses and therapies. His experience is specifically related to three main research areas: (1) full experimental characterization and modeling of novel micro- and nano-scaled contrast media for non-ionizing imaging techniques, such as US and MRI; (2) automatic extraction of information from biomedical images and signals for anatomical and functional investigations; and (3) industrial research into the development of new biomedical systems with related patenting activities at a national and international level, bridging the gap between applied research and industries in this field.

Early diagnosis of cancer through a non-ionizing approach is one of the main research objectives. In fact, cancer is a huge and growing contributor to the burden of disease and premature death worldwide: every year, more than 12 000 000 new cancer cases are diagnosed (25% in Europe) and more than 7 500 000 people die due to cancer-related causes (23% in Europe)[1]; about 25% of all deaths in the EU are attributable to cancer, and in the age range 45-64 years the percentage increases to almost 50%[2]. In addition, population growth and ageing are expected to further increase these numbers.

The only possible way to significantly improve this situation is by the introduction of completely new diagnostic methods capable of identifying tumors in their very early stages of progression, ideally before the first cancer cell is generated, that is when, as a consequence of one or more risk factors, some cell nuclei start showing specific DNA damage that is likely to give rise to tumor degeneration. Therefore, the identification of distinctive DNA alterations is crucial to better understand the mechanisms of different cancers and to detect potential genomic markers for diagnosis and prognosis[3]. In this scenario, hepatocellular carcinoma in particular has recently been indicated as one of the tumor types where a more complete understanding of the underlying genetic alterations could have a major impact on the development of new treatment strategies[4]. A potentially promising strategy could be represented by the development of

nanoparticle-based imaging agents, specifically designed to highlight possible genomic defects which are prone to subsequently develop cancer.

Non-invasive molecular imaging is an emerging field in the frame of Diagnostic Imaging which aims to develop new technologies which are able to detect processes at the molecular and cellular level in living organisms, in order to early and carefully identify and differentiate healthy tissue from pathological tissue for better diagnosis and therapy. The key feature of molecular imaging is the use of specific contrast agents that selectively identify chosen molecular targets or cellular processes, highlighting them on the corresponding image. The fundamental hypothesis of these new methods is that many diseases have a "molecular basis", whose visualization may result in a number of benefits: early diagnosis, accurate staging, real-time monitoring of therapeutic treatment outcome (through the imaging of molecular markers), better prognosis on possible disease evolutions. This approach is particularly useful in the diagnosis of tumors, since in most cases the high mortality rate associated with these pathologies is due to a "late diagnosis", done only after the tumor has reached an advanced stage.

Currently, the only diagnostic technique for which molecular imaging is already routinely used in clinics is positron emission tomography (PET), which is a highly expensive technique and, above all, involves the use of highly ionizing radiation with consequent risks for patients, operators and society. As a consequence, PET examinations can not be used for patient follow-up or for population screening purposes.

The idea of exploiting the properties of "molecular markers" has brought new perspectives for Diagnostic Imaging techniques, allowing the extension of molecular imaging applications to non-ionizing techniques, such as US and MRI, through the development and employment of innovative nano-sized "targeted" contrast agents.

ACADEMIC ACHIEVEMENTS

Sergio Casciaro started his research career in 1996 at the European Centre for Nuclear Research (CERN, Geneva, Switzerland) working on the design of the main superconducting components of the Large Hadron Collider, which nowadays represents the most important system for future fundamental research in the field of high energy physics, aimed at reproducing the "big bang" conditions at the origin of the universe. The theoretical design and experimental work conducted during his stay at CERN has been fully integrated in the final version of the system and the implemented guidelines have been instrumental for the system production in three European countries with a successful final test last year. This is undoubtedly one of the most important preliminary steps towards advancements in fundamental physics in the next century.

After research experience at the Swiss Federal Institute of Technology of Lausanne in 1999 working on fluid dynamic heat and mass transfer[5,6] and on starting up new experimental research activities, in 2000 he moved to the National Institute of Health (NIH, Bethesda, USA) in collaboration with ISBEM Institute of Brindisi and Pisa University, to work on the most advanced morphological and functional brain studies by means of MRI under the supervision of Dr. Peter A. Bandettini. He started the functional MRI brain activities in Pisa at the Institute of Clinical Physiology (IFC), the most important multidisciplinary biomedical institute of the Italian National Council of Research (CNR). From then on, all his energy and efforts have been devoted to the creation, from zero, of a multidisciplinary research group on biomedical engineering science and technology at the Lecce site of CNR-IFC. He developed an educational program on Biomedical Engineering at the Lecce University, where he recruited several young scientists for the PhD programs in Bioengineering; he implemented the research laboratories thanks to the regional, national and international grants he received in collaboration with many prestigious international scientific partners. Currently, he leads a multidisciplinary group of young researchers and PhD students, which in recent years has been actively involved in the creation and management of several research activities, and the annual organization of international scientific events.

The obtained research results, as described in detail in the following paragraphs, certify that the enormous personal and intellectual energy he invested has resulted in outstanding scientific outcomes.

During the last decade, the main research interests and activities of Sergio Casciaro have been related to the development of novel methodologies for biomedical image and signal processing, and through the introduction of new contrast media, towards innovative and minimally invasive diagnoses and therapies. Molecular, cellular, quantitative, automated and real time approaches have been of key significance in carrying out experimental and theoretical scientific investigations.

In particular, the experience gained is specifically related to the following main research areas: (1) theoretical simulations, design and full experimental characterization and modeling of novel micro- and nano-scaled contrast media for non-ionizing imaging techniques, like MRI and US[7-12] (Figure 2). These activities, whose final goal is the introduction of novel combined therapies by means of targeting, drug and gene delivery, have been performed, including custom designed phantoms for "*in vitro*" studies, as well as "*ex vivo*" experimentations and "*in vivo*" trials in animal models[13-15]; (2) automatic information extraction from biomedical images and signals for anatomical and functional investigations: automatic image segmentation and registration, tissue characterization (virtual biopsy), volume rendering for augmented and virtual reality applied to oncology radiotherapy and minimally invasive therapies (operation planning, intraoperative image guidance, training, *etc.*), functional MRI studies, employment of neural networks and expert

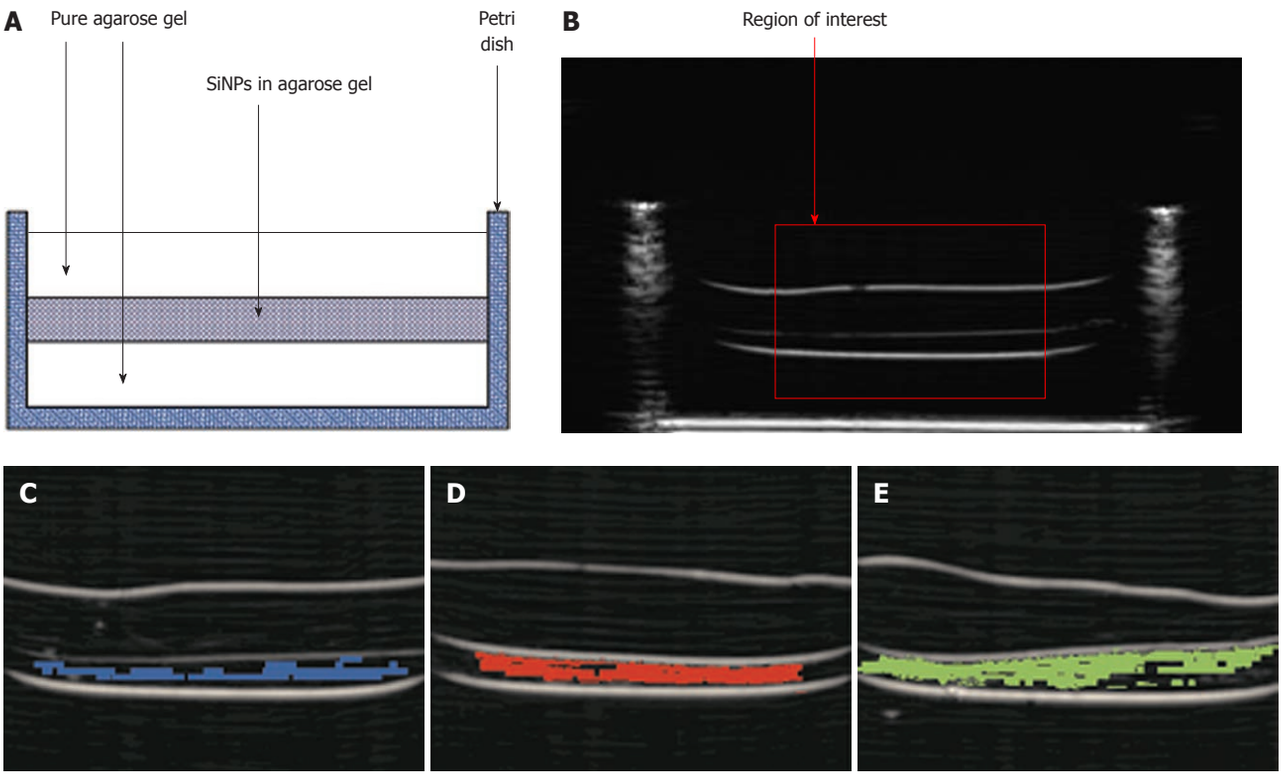

Figure 2 Example of automatic detection of accumulated Silica Nanoparticles. A: Scheme of the analyzed phantom; B: B-mode image of a control phantom with indication of the chosen ROI; C-E: Images of the analyzed ROIs with automatic detection results displayed in blue, red, and green for 150-nm, 320-nm, and 650-nm SiNPs, respectively. The sensitivity of the developed method for automatic nanoparticle detection had a maximum of 71% with 320-nm particles, whereas it was lower with both larger and smaller particles (sensitivity of 63% and 18%, respectively).

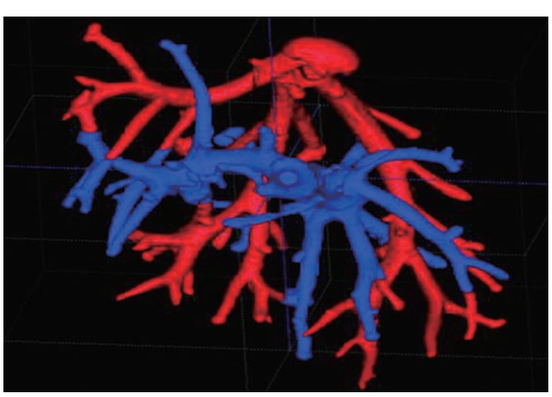

Figure 3 Example of a 3D automatic phantom image segmentation simulating liver vessel trees. The optimal algorithm configuration resulted in a vessel detection sensitivity of 100% for vessels of more than 1 mm in diameter, 50% in the range 0.5-1 mm and 14% in the 0.2-0.5 mm range. An average area overlap of 94.9% was obtained between automatically and manually segmented vessel sections, with an average difference of 0.06 mm^2. The average values of corresponding false positive and false negative ratios were approximately 8% and 3%, respectively.

systems for supporting medical decisions[16-30] (Figure 3); and (3) industrial research for the design and development of new systems and tools with the related intellectual property protection and patenting activities at a national and international level, bridging the gap between applied research and industries in this field.

The guiding principles of the conducted research activity have always been the maximum exploitation and enhancement of non-ionizing imaging techniques (US and MRI) through innovative methodologies, based on novel image and signal processing algorithms and use of the most advanced contrast media, also nanotechnology-based.

Many scientific results contributed to the advancement of the research field and this can easily be verified thanks to the acceptance of publications in major international peer-reviewed multidisciplinary scientific journals, to the granted funding and to the winning of international prizes and awards.

In the MRI field, innovative scientific contributions have been made to the advancement of depiction of venous vessels into the brain by exploiting endogenous contrast mechanisms, revealing venous vessels smaller than 1 mm and enhancing many details undetectable in conventional venograms. This approach combines non-invasiveness with high resolution images. Thanks to these research outcomes, this methodology has been used to further characterize the most important and commonly used contrast mechanism for the detection and study of neuronal activations: the Blood Oxygen Level Dependent (BOLD) contrast. Sergio Casciaro's work, has demonstrated the weakness of the BOLD mechanism in revealing neuronal electrical activity due to venous artefacts that are erroneously taken as actual brain activations, which can provide tremendous new inputs into surgical neuronal procedures. This work also received a Young

Investigator Award in Sweden.

Important contributions have also been made in the field of US imaging, both with and without the use of contrast agents. In the literature, US contrast agents (UCAs) have been studied extensively, however, most of this research has focused on the single microbubble dynamic and not on contrast agent populations. For the first time, a new interpretation model was developed by Sergio Casciaro for studying the dynamic evolution of contrast agent populations over time and characterizing the main destruction mechanisms and their changes in terms of acoustic properties which can be exploited in the fields of targeting, gene and drug delivery. Experimental studies on the behavior of contrast microbubble populations have been selected twice as finalist papers in the Young Investigator Award Competition of the "European Symposium on Ultrasound Contrast Imaging".

Another contribution is related to tissue characterization by means of spectral analysis through wavelets and independent component analysis, which is able to distinguish pathologic tissues from healthy tissues in a non-invasive and reliable way. Furthermore, all these tissue properties have been translated into artificial tissues reproducing with an excellent approximation not only the propagation of the main US signal component, but also its harmonic components normally essential for the accurate study of UCAs: "ad hoc" experimental set-ups for studying UCAs are available reducing the need for animal models and unnecessary sacrifice. This innovative technique for the manufacture of tissue mimicking phantoms for "*in vitro*" characterization of UCA behaviour was awarded the First Prize Poster Context in Chicago (IL, USA) during the "Annual Advances in Contrast Ultrasound" congress in 2005.

Finally, another important contribution was the automatic information extraction from medical images through innovative processing techniques in the case of abdominal images, without any need for user interaction, producing an important reduction in expensive manual operations. Furthermore, this method received the Best Paper Award at the ARISER Conference in 2007.

All previously summarized early scientific results received scientific recognition. First of all, by the acceptance of manuscripts in international peer-reviewed journals and conferences: from 2004 to 2009 more than sixty scientific articles were written and accepted in the field of biomedical imaging. Furthermore, four investigator awards were granted by international scientific committees and in two other cases Sergio Casciaro was a finalist in young investigator international competitions. Four patents have been also granted and several companies collaborate with Casciaro's group on industrial exploitation. Additionally, several research funds have been granted to the afore-mentioned research activities at regional, national and international level. The following are the most significant and relevant research projects in which Sergio Casciaro had scientific leadership: a FIRB project on the development of new techniques and advanced methods for the employment of UCAs in diagnostic and therapeutic applications (about 600 k€; 2003-2006); the CERSUM project (European Center for Research and Development on applications of Ultrasound in Medicine; about 1.2 M€; 2005-2008); the ARISER project focused on the implementation of Augmented and Virtual Reality techniques for development of minimally invasive surgical procedures ("Marie Curie Actions" of the 6th FP, and Sergio Casciaro has been the Scientist in Charge of the "Image and Signal Processing" Workpackage; about 500 k€; 2005-2008; see also http://www.ariser.info); a Public-Private Laboratory for the development of innovative technologies for advanced medical diagnostics (850 k€ for the past 4 years). In the last 4 years Sergio Casciaro has been nominated as Scientific Director of the annual international conference and summer school on minimally invasive technologies (MIT) of the ARISER communities, together with several invitations to give talks at international events and institutions active in the biomedical-related research field. This last activity has been of key importance for triggering the inspiration and the challenge towards future MIT and related therapies.

PERSPECTIVE

Preliminary results available in the literature support the feasibility of nanoparticle contrast agents (NPCAs) for non-ionizing cellular imaging and concurrent therapy to treat specific pathologies. An absolutely new class of "theranostic" agents are under development in our laboratory, based on biocompatible nanoparticles consisting of a rigid multi-component core (superparamagnetic compound + silica, able to introduce variation of both magnetic susceptibility and acoustic impedance in the surrounding medium) and a softer polymeric shell, whose function will be to provide a pH- and/or thermosensitive encapsulation for loaded drug molecules and to act as a bridge for the conjugation of both fluorophores capable of emitting light in the infrared region (to be exploited in intraoperative fluorescence imaging) and aptamers for the selective detection of specific disease receptors. The possibility of adding a further component, like gold nanorods, to the nanoparticle core, in order to provide a strong optical absorption due to plasmon resonance effects, employable for both hyperthermia and optoacoustic imaging purposes, will also be evaluated.

The final goal is to develop and experimentally validate a minimally invasive nanotechnology-based solution to improve cancer diagnosis accuracy and subsequent disease management, through a multimodal imaging approach and a self-tailoring and self-monitoring therapeutic treatment. The undergoing research approach will try to satisfy the actual clinical needs for risk stratification, population screening and surgeon support during interventions, offering the possibility of combining elective repeatable and cheap diagnostic examinations (US) with highly specific clinical investigations (MRI) and also with

intraoperative optical imaging modalities. The introduction of such diagnostic techniques involving nanoparticle "theranostic" agents represents a tremendous innovation compared to the state of the art of international literature. The entire systems and methods developed will then create an absolutely innovative diagnostic-therapeutic paradigm. Furthermore, it is reasonable to expect that the development of these new multimodal non-ionizing imaging modalities will allow significant improvements in the diagnostic performances of current imaging systems, and will have a strong influence on the advancements of the European technology and biomedical industry. Furthermore, the results of this research will create the basis to develop new advanced and integrated diagnostic systems, towards minimally invasive therapies of the future. Moreover, the targeting of NPCAs will allow local drug delivery with the combined use of hyperthermia systems for diagnosis and simultaneous cellular ablation of tumoral tissues towards a multi-therapy approach.

In conclusion, achievement of the ultimate goals of our main research will try to overcome PET limitations in the management of cancer pathologies by integrating diagnosis, therapy and treatment monitoring in a single non-ionizing procedure, and will open up new horizons in the field of early tumor diagnosis thanks to a revolutionary imaging approach.

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January 23-27
Radiology at Snowbird
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January 24-28
Neuro/ENT at the Beach
Palm Beach, FL, United States

February 28-29
MIAD 2011 - 2nd International Workshop on Medical Image Analysis and Description for Diagnosis System
Rome, Italy

February 5-6
Washington Neuroradiology Review
Arlington, VA, United States

February 12-17
MI11 - SPIE Medical Imaging 2011
Lake Buena Vista, FL, United States

February 17-18
2nd National Conference Diagnostic and Interventional Radiology 2011
London, United Kingdom

Februrary 17-18
VII National Neuroradiology Course
Lleida, Spain

February 18
Radiology in child protection
Nottingham, United Kingdom

Februrary 19-22
COMPREHENSIVE REVIEW OF MUSCULOSKELETAL MRI
Lake Buena Vista, FL, United States

March 2-5
2011 Abdominal Radiology Course
Carlsbad, CA, United States

March 3-7
European Congress of Radiology Meeting ECR 2011 Vienna, Austria

March 6-9
World Congress Thoracic Imaging - IV
Bonita Springs, FL, United States

March 14-18
9th Annual NYU Radiology Alpine Imaging Symposium at Beaver Creek
Beaver Creek, CO, United States

March 20-25
Abdominal Radiology Course 2011
Carlsbad, CA, United States

March 26-31
2011 SIR Annual Meeting
Chicago, IL, United States

March 28-April 1
University of Utah Neuroradiology 2nd Intensive Interactive Brain & Spine Imaging Conference
Salt Lake City, UT, United States

April 3-8
1st Annual Ottawa Radiology Resident Review
Ottawa, Canada

April 3-8
43rd International Diagnostic Course Davos on Diagnostic Imaging and Interventional Techniques
Davos, Switzerland

April 6-9
Image-Based Neurodiagnosis: Intensive Clinical and Radiologic Review, CAQ Preparation
Cincinnati, OH, United States

April 28-May 1
74th Annual Scientific Meeting of the Canadian Association of Radiologists CAR
Montreal, Canada

May 5-8
EMBL Conference-Sixth International Congress on Electron Tomography
Heidelberg, Germany

May 10-13
27th Iranian Congress of Radiology
Tehran, Iran

May 14-21
Radiology in Marrakech
Marrakech, Morocco

May 21-24
European Society of Gastrointestinal and Abdominal Radiology 2011 Annual Meeting
Venice, Italy

May 23-25
Sports Medicine Imaging State of the Art: A Collaborative Course for Radiologists and Sports Medicine Specialists
New York, NY, United States

May 24-26
Russian Congress of Radiology
Moscow, Russia

May 28-31
International Congress of Pediatric Radiology (IPR)
London, United Kingdom

June 4-8
58th Annual Meeting of the Society of Nuclear Medicine
San Antonio, TX, United States

June 6-8
UKRC 2011 - UK Radiological Congress
Manchester, United Kingdom

June 8-11
CIRA 2011 - Canadian Internventinal Radiology Association Meeting
Montreal, QC, Canada

June 9-10
8th ESGAR Liver Imaging Workshop
Dublin, Ireland

June 17-19
ASCI 2011 - 5th Congress of Asian Society of Cardiovascular Imaging
Hong Kong, China

June 22-25
CARS 2011 - Computer Assisted Radiology and Surgery - 25th International Congress and Exhibition Berlin, Germany

June 27-July 1
NYU Summer Radiology Symposium at The Sagamore
Lake George, NY, United States

July 18-22
Clinical Case-Based Radiology Update in Iceland
Reykjavik, Iceland

August 1-5
NYU Clinical Imaging Symposium in Santa Fe
Santa Fe, NM, United States

September 22-25
European Society of Neuroradiology (ESNR) XXXV Congress and 19th Advanced Course
Antwerp, Belgium

October 12-14
International Conference Vipimage 2011 - Computational Vision and Medical Image Processing
Algarve, Portugal

October 15-16
Essentials of Emergency and Trauma Radiology
Ottawa, Canada

October 23-29
2011 IEEE NSS - 2011 IEEE Nuclear Science Symposium and Medical Imaging Conference
Valencia, Spain

October 25-28
NYU Radiology in Scottsdale - Fall Radiology Symposium in Scottsdale
Scottsdale, AZ, United States

October 28-30
Fourth National Congress of Professionals of Radiological Techniques Florianópolis, Brazil

October 28-30
Multi-Modality Gynecological & Obstetric Imaging
Ottawa, Canada

November 3-4
9th ESGAR Liver Imaging Workshop
Taormina, Italy

November 15-19
EANM 2011 - Annual Congress of the European Association of Nuclear Medicine
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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

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Books

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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