The Role of Computer-Aided 3-Dimensional Analytic Tools and Virtual Microscopy in the Investigation of Radiologic-Pathologic Correlation

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● To cope with recent advances in radiologic imaging technology, a corresponding method for pathomorphologic demonstration should be developed to promote better understanding of radiologic-pathologic correlation. We attempted to obtain gross and microscopic images by using a 3-dimensional analytic tool and virtual microscopy and to link these images with multidetector computed tomography images. Surgically resected specimens were sliced to a thickness of 3 mm, and the digital images of each slice were 3-dimensionally reconstructed with RATOC TRI/3D SRF II software. Histology slides were digitized by using virtual microscopy with an Olympus VS-100. We obtained clear gross pathologic images in arbitrary cut sections of organs, and it was possible to rotate these 3-dimensional images at any angle. Furthermore, we created synchronous cut-section movies of computed tomography and gross pathologic images. Subsequently, we switched from these cut-section movies to virtual microscopy images by clicking on the hyperlink button to observe radiologic-pathologic correlation.

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In 2005, at the pathology slide conference of the Chugoku-Shikoku branch of The Japanese Society of Pathology, it was announced that digital images would be included on our homepage. The images on the home page server are plain x-ray, computed tomography (CT), magnetic resonance (MR), and gross and microscopic pathologic images including virtual microscopy (VM) images. The utilization rate of VM images, as noted at each conference, has increased from 5.9% in 2005 to 25.0% in 2007 (Table 1). At our hospital, we started weekly radiologic-pathologic conferences in November 2006 by considering the trend toward the complete digitization of all imaging modalities, including CT, MR imaging, positron-emission tomography (PET)-CT, ultrasonography, and pathomorphologic imaging.

Because it is important to integrate comprehensive imaging modalities to investigate radiologic-pathologic correlations, pathologists should update their knowledge of the recent advances in radiologic technology, including 3-dimensional (3-D) image processing and functional imaging. A corresponding method for pathomorphologic demonstration should be provided to promote better understanding of radiologic-pathologic correlation.

In the present study, we obtained gross and microscopic pathologic images and attempted to reconstruct them by using a 3-D analytic tool and VM as follows: (1) acquiring cut-section movies and 3-D movies of gross pathologic images, (2) acquiring synchronous cut-section movies of CT (or MR) and gross pathologic images, and (3) linking these synchronous movies to “Unified VM imaging,” which enables the visualization of several VM images of an entire cut section as a single VM image.

MATERIALS AND METHODS

The formalin-fixed specimens from cases of surgically resected tumor were sliced to a thickness of 3 mm by using an organ slicer. During slicing, clay was frequently used to fix the specimens. The images of each slice were captured with a digital camera and 3-dimensionally reconstructed by using the TRI/3D SRF II software (RATOC System Engineering Co, Ltd, Tokyo, Japan). This process involved the following steps: (1) loading the images of each slice, (2) adjusting the 3-D slice position, (3) interpolation, (4) color extraction of the specimen and segmentation processing, (5) removing the unnecessary parts of the images (ie, the background), (6) observing the cut sections of the slices and the 3-D images from various directions, and (7) making movies (cut sections, 3-D rotations, synchronization) and analyzing the image data by using the measurement function of the TRI/3D SRF II software. Viewer software for TRI/3D SRF II was used to acquire cut-section and 3-D images from the volume data and to observe them from arbitrary directions.

Histologic slides of gross lesions were prepared and were digitized by VM with VS-100 (Olympus, Tokyo, Japan). Automated whole-slide image capture was performed by using a charge-coupled device camera (0.32/pixel; Olympus) outfitted with an Olympus UPlanSApo 20×, 0.75 numerical aperture objective lens. We attempted to link the movies with the VM images.

The registration algorithms for making synchronous movies of CT images and gross pathologic specimen images are as follows.

Step 1: To make movies of gross pathologic slices and to obtain CT volume data comprising the surgically resected organ images from radiology information systems/picture archiving and communication systems (RIS/PACS).
breast specimen revolves continuously, thus enabling its visualization from all directions. Moreover, the movie can be stopped at the desired angle. The red mass seen in the figure shows a breast cancer, and tumor extension into the resected breast specimen can be observed. Hence, the likelihood that the patient will be cured can be assessed. Using the measurement function of the TRI/3D SRF II software, we calculated the volumes of the breast cancer (2246 mm³) and the entire resected specimen (53398 mm³).

Case 2: Cardiac Tumor

A 63-year-old man underwent tumor resection for a cardiac myxoma in the left atrium (tumor size, 4.7 × 4.6 × 3.3 cm).

Figure 2 shows an image from a 3-D movie of the cardiac myxoma. The left portion of the mass seen in the image was adherent to the left atrial septum. The tumor can be visualized from all directions and can be evaluated from the desired angle. We can use different colors to differentiate the myxoma from the nonneoplastic atrial septum (not shown in the figure). In addition, we can also change the transparency of the tumor and/or nonneoplastic portion and observe the relation between myxoma and nonneoplastic portion from all directions.

Case 3: Liver Cancer

A 73-year-old man underwent partial hepatectomy for hepatocellular carcinoma located in segment S5. Nonalcoholic steatohepatitis (non-B, non-C) was also seen.

Figure 3, A, shows images from synchronous cut-section movies of enhanced CT and gross pathologic images. These movies are similar to those described in the legend for Figure 1, B. Virtual microscopy images of the liver histology slides can be seen by clicking on the hyperlink button (Figure 3, B). Multiple image documents can be simultaneously visualized by using the synchronization process of the Olympus VS-100 and can be easily compared. Clinicians viewed these images through network connections on remote workstations located in our hospital’s information office.

Clear gross pathologic images of arbitrary cut sections of specimens were successfully acquired and it was possible to rotate the 3-D images at any angle in all cases. Furthermore, we were able to create synchronous cut-section movies of CT and gross pathologic images to observe radiologic-pathologic correlation. Subsequently, we switched from viewing these movies to viewing VM images by clicking on the hyperlink button (movies available at http://www.ratoc.com, accessed November 1, 2008).

COMMENT

Recent advances in the techniques in digital pathology have enabled the almost complete preservation of gross and microscopic image findings, including the links to radiologic images, and the effective investigation of radiologic-pathologic correlation. The fundamental principles for volume data processing in 3D SRF II are volume rendering (3-D expression), multiplanar reconstruction (cut sections), and maximum-intensity projection. The TRI/3D SRF II software enables the processing of 3-D images at any level in the human body, from the organ to the histologic level.

Our digital system has some advantages over other registration systems or methods. With this system, we can obtain clear images of gross pathologic arbitrarily cut sec-

### Table 1. The Use of Imaging on Web Site for the Meeting of the Chugoku-Shikoku Branch of the Japanese Society of Pathology (2005–2007)

<table>
<thead>
<tr>
<th>Meeting, y/mo</th>
<th>Imaging, total (No., %)</th>
<th>pGross, No. (%)</th>
<th>VM image, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>87th, 2005/06</td>
<td>17 (0, 0) 5 (29.4) 1 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>88th, 2005/11</td>
<td>21 (2, 9.5) 5 (23.8) 3 (14.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>89th, 2006/02</td>
<td>18 (1, 5.6) 1 (5.6) 4 (22.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90th, 2006/06</td>
<td>17 (3, 17.6) 4 (23.5) 4 (23.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>91st, 2006/11</td>
<td>13 (1, 7.7) 1 (7.7) 3 (23.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>92nd, 2007/02</td>
<td>21 (0, 0) 1 (4.8) 6 (28.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>93rd, 2007/06</td>
<td>20 (1, 5.0) 3 (15.0) 5 (25.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: pGross, gross pathologic imaging; VM, virtual microscopy; y/mo, year/month.

* Plain x-ray, computed tomography, and magnetic resonance imaging.
tions of organs, and the 3-D images can be rotated at any angle. Furthermore, we can create synchronous cut-section movies of CT and gross pathologic specimen images in the arbitrarily cut section planes. Subsequently, we can observe the radiologic-histopathologic correlation by switching from these movies to VM images by clicking on the hyperlink button (Table 2). However, a limitation is that a manual process is required to perfectly adjust CT image planes to gross pathologic specimen image planes by viewing each image on the RIS/PACS monitor and comparing it with the gross pathologic specimen image. Computation of the plane adjustment process will be possible henceforth because real-time virtual sonography is now widely used as an excellent navigator for radiofrequency ablation for cancer therapy. This sonography system generates multiplanar reconstruction images in real time by using the Hitachi medico EUB-8500 (Tokyo, Japan), which is equipped with a probe and matches the images on the monitor with the actual sonography image to show a cross-sectional view with the tumor displayed on a multiplanar reconstruction image.1

With the major advancement in spiral CT in recent years, 3-D CT imaging can now be performed by using different reconstruction methods to improve diagnostic accuracy.2 Because the rate of minimally invasive surgery for various diseases is increasing, a more precise evaluation of the correlation between CT/MR imaging and the pathomorphologic findings of various diseases is necessary. Kadoya et al3 analyzed the MR imaging appearance of hepatocellular carcinoma in relation to its macroscopic

Figure 1.  A, Two-dimensional cut sections of the resected breast specimen: XY (top left), XZ (bottom left), and YX (bottom right) and an arbitrary cut section (top right). B, Images from synchronous cut-section movies of enhanced computed tomography image (left) and gross pathologic image (right). C, Images from a 3-D movie of the resected breast specimen. The red mass is the breast cancer.

Figure 2.  An image from a 3-D movie of the resected cardiac myxoma specimen. The left portion was adherent to the left atrial septum.

Figure 3.  A, Images from synchronous cut-section movies of enhanced computed tomography image (left) and gross pathologic image (right) of the resected liver specimen. B, Virtual microscopy (VM) images of the liver, including a whole cut-section (top) and an imaginary “Unified VM image” (bottom).
features (eg, capsule and mosaic pattern) and histologic findings.

The third objective of the present study was to make synchronous 3-D movies of the gross radiologic and pathologic images with links to the "Unified VM image" (Figure 3, B). Although this objective has not yet been achieved, currently it is possible to link the gross pathologic images to the corresponding VM images and examine their interrelationship. Precise 3-D delimitation of a tumor is essential for planning a therapy to decide the extent of tumor removal and the radiation fields to be applied. Daumas-Duport et al4 defined the following 3 categories of 3-D configuration of gliomas: noninfiltrating solid gliomas, infiltrating gliomas with tumor tissue proper, and infiltrating gliomas without tumor tissue proper. Johnson et al9 correlated the findings of postmortem MR imaging with the neuropathologic findings in human cerebral gliomas by using the whole-brain specimens obtained during routine autopsy. They demonstrated 4 kinds of morphologic findings, namely, those on postmortem MR images, on photographs of whole-brain cross section, on photographs of stained whole-brain cross section (Weil stain), and on photomicrographs (stained with hematoxylin-eosin). They also compared the extent of the tumor observed on MR images with the histologic tumor boundaries and classified the MR imaging findings as underestimated, equal, or overestimated. For conducting studies with large specimens, such as whole-brain sections and whole-liver sections, our method of integration of images with large specimens, such as whole-brain sections and whole-liver sections, our method of integration of images obtained at all levels of the human body, including gross pathologic and VM images, will prove to be efficient and precise and will thus help accomplish the various objectives of imaging studies (Table 2).

Thus far, we have stated the method for single-organ imaging. However, during imaging diagnosis in routine clinical practice, radiologists observe whole-body images of all organs, and the findings of the interrelationships between these organs are important in imaging diagnosis. We applied our image integration method to transverse axial sections from 2 autopsy cases to examine the relation between the thoracic organs. Although CT/MR imaging is increasingly being used for the evaluation of chest diseases, radiography still remains an important modality. Our image integration method provided useful morphologic information for understanding the concept of "lines and strips," which are formed from the configurations and interrelationships of the anatomic structures comprising the lungs, mediastinum, and pleura.

Autopsy imaging has been attempted at some research centers. They reported that this technique provides critical and supplemental information for conventional autopsy.7,8 A combination of autopsy imaging and autopsy with transverse axial sections of the desired portions and the integration of these images by using our image integration method will prove to be more informative.

Since functional imaging with radionuclides does not provide the fine structural details obtained by anatomic imaging, whole-body positron emission tomography–CT fusion images are required for accurate imaging diagnosis.9 A combination of positron emission tomography–CT fusion images and VM images with our image integration method will prove to be more informative for studies on surgical resection and autopsy specimens.

Regarding the usefulness of our present study on image integration, the study provides both radiologists and pathologists an impetus to more strongly focus on radiologic-pathologic correlation in our weekly conferences on imaging diagnosis.

Furthermore, all the integrated images mentioned thus far will prove to be a valuable library resource for pathologists, radiologists, and other medical specialists. We should make conscious efforts to obtain information about the integration of all levels of "morphologic diagnostics," from molecules to the whole human body, since the highest achievements can be expected when the diagnostics of different levels meet.

CONCLUSION

We expect this study to act as a stimulus for both radiologists and pathologists to focus more closely on radiologic-pathologic correlations and improve their skills regarding imaging diagnosis.

We express our deep appreciation to our colleagues Kyoko Hino, CMT, and Eriko Ohizumi, CMT, for their valuable technical contribution.

References

Table 2. Integration of Images of Different Human Body Levels: Their Characters and Relations

<table>
<thead>
<tr>
<th>Images (Human Body Levels)</th>
<th>Image Characters (Tools)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologic imaging (organs)</td>
<td>Volume data (CT, MR)</td>
</tr>
<tr>
<td>↑ Simultaneous reading with physical findings and case history</td>
<td></td>
</tr>
<tr>
<td>Gross pathologic imaging (organs, tissues)</td>
<td>Volume data (TRI/3D SRF, II; RATOC)</td>
</tr>
<tr>
<td>↑ Linking in a moment</td>
<td></td>
</tr>
<tr>
<td>Microscopic pathologic imaging (tissues, cells)</td>
<td>WSI (virtual microscopy)</td>
</tr>
<tr>
<td>Molecular/genomic imaging (molecules)</td>
<td>WSI of IHC specimens</td>
</tr>
<tr>
<td>(DNA/RNA)</td>
<td>WSI of ISH specimens</td>
</tr>
</tbody>
</table>

Abbreviations: IHC, immunohistochemistry; ISH, in situ hybridization; MIP, maximum-intensity projection; MPR, multiplanar reconstruction; VOR, volume rendering; WSI, whole-slide imaging.

* Multidetector computed tomography (CT), magnetic resonance (MR).