PhenX Toolkit

Data Collection Worksheet

Please Note: The Data Collection Worksheet (DCW) is a tool to aid integration of a PhenX protocol into a study. The PhenX DCW is not designed to be a data collection instrument. Investigators will need to decide the best way to collect data for the PhenX protocol in their study. Variables captured in the DCW, along with variable names and unique PhenX variable identifiers, are included in the PhenX Data Dictionary (DD) files.

Part I: Computed Tomography—Liver Fat/Hepatic Steatosis

Multidetector Computed Tomography (MDCT) Scan Protocol

Individuals were scanned using an eight-slice MDCT (LightSpeed Ultra, General Electric, Milwaukee, WI, USA) in the supine position and amounted to a total effective radiation exposure of 2.7 mSv. Twenty-five contiguous 5-mm thick slices (120 kVp, 400 mA, gantry rotation time 500 ms, table feed 3:1) were acquired, covering 125 mm above the level of S1; raw data were reconstructed using a 55 cm field of view. In the chest, 48 continuous 2.5-mm thick slices (120 kVp, 320/400 mA [for < and >100 kg of body weight, respectively], gantry rotation time 500 ms, and temporal resolution 330 ms) were acquired during a single breath hold and reconstructed using a 35 cm field of view. A calibration control (phantom, Image Analysis, Lexington, KY, USA) with a water equivalent compound (CT-Water, Light Speed Ultra, General Electric, Milwaukee, WI, USA) and calcium hydroxyapatite at 0 mg/cm^3, 75 mg/cm^3, and 150 mg/cm3 was placed under each patient. We used the 150 mg/cm^3 phantom to standardize all liver measurements, as this phantom had the least percentage error in its measure (data not shown).

Protocol Development

We measured the Hounsfield units (HUs) of the liver, spleen, and paraspinal muscles and an external phantom control. In order to determine the optimal number of CT slices to interpret, we measured two separate areas over an area of 100 mm^2 in the liver, intentionally avoiding blood vessels in the liver. We also measured two separate areas in the spleen and one area each in the paraspinal muscles, avoiding fat planes. We conducted the measures in two abdominal and two chest CT slices per individual in a total of 10 individuals. In order to determine whether to use the chest or abdominal scans for the fatty liver measurement, we measured six separate areas in the liver, three in the spleen, and one each of the paraspinal muscles, and determined whether the variation in these measurements was less for the chest or abdominal scans. In order to determine the most parsimonious number of measures necessary in the liver, spleen, and paraspinal muscles, we compared three versus six measured areas in the liver and two versus

three measures in the spleen. Our final protocol used three measures of at least 100 mm2 in the liver, two in the spleen, one in the left and one in the right paraspinal muscles, and one in an external phantom. Two independent observers (EKS and MCF) analyzed the same set of computed tomograms independent of each other and were blinded to participant characteristics. One observer repeated reading the scans 2 weeks after the initial period of reading (EKS) to determine intrareader correlations.

Part II: Computed Tomography—Organ Volumes

All patients were scanned on a General Electric® Lightspeed QX multislice scanner (Waukesha, WI, USA) or a General Electric® CT/I single-slice scanner. Scanning parameters depended on the clinical indication for the study, and all techniques were part of established clinical protocols. Consistent with this, all patients were scanned at 120 kVp, and the section thickness varied between 5 and 10 mm for all subjects. Most studies were contrast enhanced.

Analysis of patient images

The abdominal CT images were downloaded from our research PACS system (eFilm, eFilm, Inc., Toronto, ON, Canada) and transferred to a PC workstation. Studies were viewed on the workstation monitor for review of DICOM header information (age, sex, display field of view, and section thickness), which was subsequently recorded in a spreadsheet. The image files were saved sequentially as DICOM files. For organ identification (i.e., segmentation), images were displayed on a computer monitor with a resolution of 1280 X 1024 pixels. Custom mouse-and-cursor software, written in C and using a Windows 2000 platform (C/C++ 5.0, Microsoft Corporation, Redmond, WA, USA) enabled handoutlining of the ROIs. Each image was magnified by a factor of 2 during the outlining process to reduce eye fatigue and improve positioning fidelity of the mouse/cursor pointing system. Window and level settings were selectable in the custom software, but settings were typically close to a window of 400 and a level of 30. All outlining was performed by a single investigator (E.M.G.; at the time, a fourth-year medical student) trained to recognize the relevant organ boundaries by a board-certified radiologist specializing in abdominal imaging (J.P.M.). The outlining of more than 18,000 organ boundaries took place over a period of 9 months, and lengthy outlining sessions were avoided to reduce fatigue.

Each of the solid abdominal organs and L1 were located and subsequently hand-outlined by using 10-pixel (~4–6 mm) long-line segments to trace anatomic boundaries. For visual clarity during the outlining procedure, the program was written to connect adjacent points with a colored line (a different color for each ROI). Although tracing the outline of the spleen (SP), right and left adrenals (RA and LA), and pancreas (PC) was straightforward, certain rules were used in the outlining of the liver (LV), right and left kidneys (RK and LK), and L1.

With regard to the liver, the inferior vena cava was excluded from the outline, but the hepatic veins draining into the inferior vena cava were included because they were intraparenchymal. Further, the portal venous system was included in sections where it appeared intrinsic to the liver but was not included on the sections where it was clearly seen extrinsic to the liver (i.e., where it might reasonably be surgically cut in a transplant or autopsy). The liver has several fissures that are visible on CT images. When the fissures opened to the abdominal cavity or were fairly large, they were excluded; otherwise, they remained as a part of the liver parenchyma.

In the kidneys, the collecting system and vasculature were not traced, leaving only the cortex and medulla for volume calculations. Although volume changes in the kidneys can sometimes occur after the injection of iodinated contrast agent, the use of low-osmolar contrast agent (as is done at our institution) and the rapid imaging protocols were thought to reduce the influence of such changes, and these effects are almost certainly smaller than normal anatomic variation between individuals (even after correction for height and weight).

We chose to use L1 as an anatomic landmark for several reasons: (a) early work on organ volume calculation, using cross-sectional imaging, found that normalizing data to indices based on L1 account for body habitus (Heuck, Maubach, Reiser, et al., 1987; Gourtsoyiannis, Prassopoulos, Cavouras, & Pantelidis,1990); (b) L1 is easily identifiable by human observers and is likely to be of only moderate difficulty to locate automatically; (c) variation in the orientation of L1 has little effect on area and diameter (e.g., a 10-degree change would lead to a 1.5% difference in area); and (d) almost all abdominal CT studies include L1. We chose to circumscribe L1 with a dorsal cutoff through the pedicles at the widest diameter of the spinal canal, a highly reproducible method. Table 1 lists the organs studied in this project and provides a key for abbreviations used.

Table 1. Organs and their abbreviations

RK	Right kidney
LK	Left kidney
L1	Lumbar vertebra 1
LV	Liver
LA	Left adrenal

RA	Right adrenal
Sp	Spleen
PC	Pancreas

The trends in organ volume as a function of age were assessed with linear regression. Compared with body mass and height, organ volume was found to have minor correlations ($0.44 > r > 0.08$) with age. A minimum of data correction was sought to increase the utility of the data compiled. Even though corrections for height and weight of the patient seemed obvious in light of the wide range in patient size, age dependency was determined to be a much smaller effect. Therefore, no age corrections were performed on these data.

Volume calculation

The volume calculation for the ROIs was implemented from the boundary data. The individual boundary points correspond to individual pixels in the image, with each point spaced approximately 10 pixels apart. Software was written which summed the number of pixels inside the outline boundaries. Single pixel area (s^2) was computed from the known pixel width, s. The organ area (cm^2) was computed from each outline as the product of the number of pixels (N) in the outline and the pixel area for that image. The volume (V) of an organ on a single section j was calculated as the product of the organ area and the CT section thickness (T_j where $V_j = T_j N_j s_j^2$). The total volume (V_{total}) for each organ was computed by summing the volumes from each section that included that organ ($V_{total} = \Sigma V_j$).

Anthropometric measurements

Previous research has shown that the volumes for many of the abdominal organs can be correlated to a persons sex, height, and weight. Unfortunately, height and weight values were not available for a number of the subjects, even after careful review of their medical records. For these patients, a technique developed previously was used to estimate height and weight from ROI parameters measured on a single CT image. Additional ROIs were outlined for these patients, and predictive equations for each patients height and weight were used. These methods are described elsewhere (Geraghty & Boone, 2003).

Organ volume was found to be far less dependent on age than on height or weight; therefore, to keep the corrections to a minimum, age dependency of organ volume was not attempted.

Phantoms

Organ volumes measured by imaging methods have been validated previously by techniques requiring surgical removal of the organ (Schiano, Bodian, Schwartz, et al., 2000; Breiman, Beck, Korobkin, et al., 1982; Moss, Friedman, & Brito, 1981). However, changes in blood volumes for in vivo versus ex vivo organs can lead to inaccuracies when using this technique. To estimate the accuracy of our volume determinations, balloons with known volumes were scanned and measured. Five balloons of different shapes (spheres, tubes, and wiggly tubes) and sizes were filled with tap water to a volume close to the mean volume for each organ (adrenal, kidney, pancreas, spleen, and liver). Different amounts of iodine-based contrast agent were added to each balloon. All balloons were placed in a water-filled tub in a pseudo-anatomic manner. Balloons were scanned on both scanners used in this study for the accrual of patient images. A technique of 120 kVp and 300 mAs was used. The display field of view was 36 cm. Section thickness varied depending on which CT scanner was used. Balloons were scanned at 2.5 and 5 mm on the GE Lightspeed multislice scanner, and those imaged on the GE CT/I single-slice scanner were sectioned at 5 and 7 mm. Images were obtained helically and axially and were reconstructed according to the standard abdominal protocol that was used for acquisition of the patient images. After imaging, balloons were cut and opened into appropriately sized graduated cylinders to more accurately measure their volumes.

Intraobserver variability

Intraobserver variability in outlining ROIs was studied. Five CT examinations were reevaluated and redundant ROIs were traced (by E.M.G.). For this experiment, we used the total body circumference at the level of L1. These data were used to assess the precision (reproducibility) of the manual outlining procedure.

Interobserver Variability

Hand-outlining of organs involves dexterity of the hand and the eye, and subjective decisions concerning the delineation of low-contrast edges also need to be made. To evaluate the role that interobserver variability has on volume determination, two observers (E.M.G. and J.P.M.) independently handoutlined each of eight abdominal organs on the same patients CT study. Comparisons were made between each observers calculated organ volumes, and the average differences were reported.

Statistical analysis

All organ volume data analysis was performed independently by sex. To reduce the dependence of patient height and weight on organ volumes, multiple linear regression (single-value decomposition ((Press, Flannery, Teukolsky, & Vetterling, 1988)) analysis was performed such that $V_{measured} = a + F_{ht}$ X height + F_{wt} weight.

International standards for body habitus were used (REM Task Group IC2, 2002),

corresponding to a standard man (1.76 m, 73 kg) and a standard women (1.63 m, 60 kg). Using the height and weight dependencies established by multiple linear regression analysis (specifically, the slopes F_{ht} and F_{wt}), each patients organ volumes were corrected:

$$V_{corrected,j} = V_{measured,j} + F_{ht}\,(H_{std} - H_j) + F_{wt}(W_{std} - W_j)$$

where H_{std} = 1.63 m and W_{std} = 60.0 kg for women and H_{std} = 1.76 m and W_{std} = 73.0 kg for men. The *j* subscript refers to the *j*th patient.

The corrected volumes were analyzed with statistical software (Sigma Stat, Jandel Scientific, Corte Madera, CA, USA), and the Kolmogorov-Smirnov test was used to determine normality at $p > 0.05$. Datasets that pass the Kolmogorov-Smirnov test are consistent with data patterns drawn from a normal (gaussian) distribution, so using a Gaussian distribution to model these data is appropriate. Additional data analyses were performed with spreadsheet software and custom C programs (Excel and Visual C/C++ 5.0, Microsoft Corporation).

Protocol source: https://www.phenxtoolkit.org/protocols/view/190501