Three-Dimensional Segmentation of the Tumor in Computed Tomographic Images of Neuroblastoma

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Segmentation of the tumor in neuroblastoma is complicated by the fact that the mass is almost always heterogeneous in nature; furthermore, viable tumor, necrosis, and normal tissue are often intermixed. Tumor definition and diagnosis require the analysis of the spatial distribution and Hounsfield unit (HU) values of voxels in computed tomography (CT) images, coupled with a knowledge of normal anatomy. Segmentation and analysis of the tissue composition of the tumor can assist in quantitative assessment of the response to therapy and in the planning of delayed surgery for resection of the tumor. We propose methods to achieve 3-dimensional segmentation of the neuroblastic tumor. In our scheme, some of the normal structures expected in abdominal CT images are delineated and removed from further consideration; the remaining parts of the image volume are then examined for the tumor mass. Mathematical morphology, fuzzy connectivity, and other image processing tools are deployed for this purpose. Expert knowledge provided by a radiologist in the form of the expected structures and their shapes, HU values, and radiological characteristics are incorporated into the segmentation algorithm. In this preliminary study, the methods were tested with 10 CT exams of four cases from the Alberta Children's Hospital. False-negative error rates of less than 12% were obtained in eight of the 10 exams; however, seven of the exams had false-positive error rates of more than 20% with respect to manual segmentation of the tumor by a radiologist.

KEY WORDS: 3D image segmentation, neuroblastoma, computed tomography, fuzzy connectivity, tumor segmentation

INTRODUCTION

Neuroblastoma is a malignant tumor deriving from cells of neural crest origin that give rise to the sympathetic nervous system.¹ Therefore, neuroblastoma may arise anywhere along the

sympathetic ganglia,² including the adrenal medulla (the most common site), the neck (stellate ganglia), the posterior mediastinum (located posterior to the heart, anterior to the vertebral column, and superior to the diaphragm), and the pelvis (organ of Zuckerkandl).^{3,4} Neuroblastic tumors belong to an intriguing and enigmatic group of neoplasms that, of all human malignant neoplasms, have the highest rate of spontaneous regression. Yet, the prognosis remains extremely poor when neuroblastoma occurs as disseminated disease in children.^{5,6}

The extent of neoplastic disease can be grouped into three types of sympathetic-chain ganglion cell lesions. Neuroblastoma is the most immature and

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malignant form, usually appearing before the age of 5 years. Ganglioneuroblastoma, having a peak incidence between the ages of 5 and 10 years, is a more mature form, retaining malignant characteristics. Ganglioneuroma is well differentiated and benign, typically presenting after 10 years of age.⁷

Neuroblastoma is the most common extracranial, solid, malignant tumor in children,⁸ accounting for 8–10% of all childhood cancers⁵ and 15% of all cancer-related deaths in the pediatric age group.² The median age of diagnosis is 2 years, with 75% of the diagnosed patients being under the age of 4 years, and fewer than 10% being over the age of 10 years.⁸ In the United States, approximately 650 children are diagnosed with neuroblastoma each year.⁹ Neuroblastoma is the most common cancer of infancy, with an incidence rate almost double that of leukemia, the next most common malignancy occurring during the first year of life.⁹ In Canada, neuroblastoma is the leading cause of cancer death in the age group 1–4 years, accounting for 21% of deaths, and its contribution to death due to cancer remains substantial (11%) for 5- to 9-year-old children.¹⁰

Mass screening investigations have been performed in Japan, Europe, and North America. Although the number of detected instances increased significantly with screening, many had a favorable prognosis. The favorable prognosis is associated with a high rate of spontaneous regression or maturation of neuroblastoma into benign ganglioneuromas.¹¹ Although the studies are not conclusive, the screening process has been observed to lead to overdiagnosis and unnecessary treatment. The data suggest that the benefit of screening on mortality is proportionally small.¹² Woods et al.¹³ advised that widespread screening for neuroblastoma not be adopted anywhere in the world.

Sixty-five percent of neuroblastic tumors are located in the abdomen, and approximately two-thirds of them arise in the adrenal gland. Fifteen percent of neuroblastic tumors are thoracic, usually located in the sympathetic ganglia of the posterior mediastinum. Ten to twelve percent of disseminated neuroblastic tumors have an unknown site of origin.⁸ The main determinants of prognosis are the patient's age and the stage of the disease at diagnosis. The site of the primary tumor also has relevance to the overall prognosis. Tumors arising in the abdomen and pelvis have the worst prognosis, of which adrenal tumors result in the highest

mortality. Thoracic neuroblastoma has an overall 61% survival rate, compared to the 20% survival rate of abdominal neuroblastoma.⁸

Radiological Analysis of Neuroblastoma

The radiology of neuroblastoma has been studied extensively.^{1,8,14–16} Radiological analysis is an integral and necessary part of diagnosis and staging of neuroblastoma, and is essential in the evaluation of the response to treatment.

The International Neuroblastoma Staging System (INSS)^{17,18} provides global, uniform criteria for staging of the neuroblastic tumor. The INSS classifies the extent of neuroblastoma into four stages, taking into account clinical and radiological findings, radiographic and scintigraphic studies, tumor resectability (resectability implies removal without a radical surgical procedure, i.e., without removing vital organs, compromising major vessels, or disfiguring the patient), extension of the tumor past the midline (the vertebral column), lymph node involvement, and dissemination into other organs. Stage 1 defines a localized tumor with complete gross excision, with or without microscopic residual disease, and is associated with a favorable outcome. The definitions of stage 2A and stage 2B imply a local tumor of incomplete gross excision and some lymph node involvement. Stage 3 is defined as an unresectable unilateral tumor infiltrating across the midline. Patients with primary tumor dissemination into distant organs are classified as stage 4. Stage 4S includes a localized primary tumor, as defined by stage 1, 2A, or 2B, but with dissemination into certain organs; it is limited to infants less than 1 year of age.^{17,18}

For the assessment of the extent of the disease and the primary tumor, computed tomography (CT) and/or magnetic resonance (MR) imaging (MRI) and 3-dimensional (3D) measurements are recommended.¹⁸ Diagnostic imaging is a mandatory guide to resectability, prognosis, and therapeutic strategies.¹ MRI is considered to be a noninvasive, painless, and well-tolerated imaging modality for evaluating children without the use of ionizing radiation,¹⁹ and for many investigators, it has become the modality of choice.^{20,21} MRI is more accurate than CT when the primary tumor has disseminated into distant organs (stage 4),²² as it provides excellent soft-tissue resolution and clearly demonstrates bone marrow metastases.²¹ However,

with the advent of helical CT scanning, intravenous contrast material is optimized, acquisition times are substantially less than that of MR scans,²³ and CT scans are more cost-effective. (MR imaging of pediatric patients often requires sedation, which increases the total time needed for the imaging procedure.) Also, CT is able to detect calcifications, a finding in favor of neuroblastoma and against Wilms tumor.¹⁵ MRI is unable to identify calcium directly; however, calcifications may be detected on MR images in the form of signal voids.¹ CT scans can, with high sensitivity and accuracy, define the extent and location of the primary tumor, and are useful for detecting contiguous or distant lymph node involvement, which are important considerations in staging and assessing resectability.¹⁹ CT of the primary site of the disease and the adjacent body cavities is, therefore, mandatory.²⁴ Regardless, Foglia et al.²⁵ expressed the opinion that one could not rely on diagnostic imaging alone to make decisions regarding the necessity for and the timing of delayed surgery.

In CT exams, abdominal neuroblastoma is seen as a mass of soft tissue, commonly suprarenal and paravertebral, irregularly shaped, lobulated, extending from the flank toward the midline of the abdomen, and lacking a capsule. The mass tends to be inhomogeneous as a result of tumor necrosis, and contains calcification in approximately 85% of patients. Calcifications are usually dense, amorphous, and mottled in appearance.⁸ Sometimes, neuroblastoma presents areas of central necrosis, shown as low-attenuation areas that are more apparent after contrast enhancement (see Fig. 1a).^{1,2}

Neuroblastoma occasionally behaves in an unpredictable manner, but usually follows one of three clinical courses: spontaneous regression, differentiation (maturation) from a malignant tumor to a benign ganglioneuroma, and progressive malignant disease.³ Current therapy for neuroblastoma is multimodal, incorporating chemotherapy, radiotherapy, and surgery.

Complete surgical resection of the primary tumor is the ultimate goal and is recommended whenever possible.² However, the primary tumor of a patient with advanced neuroblastoma can be unresectable, if there is a risk of damaging vital structures in the procedure (notably when the mass encases the aorta). Therefore, surgery is delayed until the tumor, in response to therapy, has shrunk to permit resection. Figure 1 shows the

evolution of a case of neuroblastoma in response to therapy. The tumor has progressed from diffuse, malignant, active disease (viable tumor) in (a); to a heterogeneous mix of dead tissue (necrosis), calcification, and viable tumor in (b); and to a benign, calcified mass in (c).

The International Neuroblastoma Response Criteria (INRC)^{17,18} provide parameters to standardize the description of the response to therapy. The assignment of a given level of overall response involves a thorough assessment of both primary and metastatic tumor sites. Six levels ranging from complete response (CR) to progressive disease (PD) are used to describe the response to therapy.

Computer-Aided Analysis of Tumors

Tumor volume at diagnosis is an important prognostic factor. Brodeur et al.¹⁸ recommend that the volume of the primary tumor and large metastases be established to the best approximation, and sequentially used to determine response to therapy. In addition, volume change may indicate response to therapy, and can be used as an index of the extent of the disease.^{26,27} Many methods and strategies have been proposed to estimate tumor volume with varying accuracy,²⁸ including the ellipsoid method.²⁹ However, geometric models are inaccurate when used to quantify the volume of irregularly shaped biological structures.²⁶ Another approach is the sum of areas, where planimetry is applied to contiguous CT slices that include the tumor. Volume calculation is performed by manually mapping out the tumor area on every CT section via a cursor, and then multiplying the area by the section thickness to yield the section volume. The sum of the section volumes yields the total tumor volume. This is an accurate but time-consuming technique.³⁰ The 3D volume method,³¹ where the computer is used to interpolate between individual sections to create the actual tumor shape, gives the most accurate representation of the overall tumor. However, tumor edges are still manually defined. Ultimately, accuracy is mainly limited by the ability to define a precise boundary around the mass.²⁶

Tumor definition and diagnosis require an analysis of the spatial distribution of CT Hounsfield unit (HU) values, coupled with a knowledge of normal anatomy. Computer-aided analysis could improve radiological analysis of neuroblas-

Fig 1. (a) Initial diagnostic CT image of a 2-year-old male patient (April 2001). (b) Intermediate follow-up CT image (June 2001). (c) Presurgical CT image (September 2001). Also shown are the contours of the tumor mass as drawn by a radiologist (G.S. Boag). A consistent spatial cross section is displayed. Note the progression of the tumor from an active or viable tumor in (a), to a mixture of necrosis and calcification in (b), and to a predominately calcified mass in (c).

toma by offering more sophisticated and accurate measures of information in the image data. Automatic or semiautomatic segmentation of the tumor mass could assist in diagnosis and evaluation of response to therapy, aid in improving reproducibility, and remove interobserver as well as intraobserver variability. Quantitative analysis could be used to assess the response to therapy

and aid in the planning of delayed surgery for resection of the tumor.

Once segmentation of the tumor mass has been accomplished, the tissue content of the mass may be estimated via statistical modeling and analysis. Ayres et al.²⁷ proposed a statistical parametric model (Gaussian mixture model) for the tissue composition of the tumor, and an expecta-

tion-maximization algorithm to estimate the parameters of the model. This model can quantitatively assess, using segmented image-based examinations, the amount of viable tumor, necrosis, nonviable tumor, calcification, and other tissues in a given tumor mass. Frequently, the tumor in neuroblastoma undergoes necrosis, seen as an increase in the relative volume of tissue with low attenuation values. Necrotic tissue may subsequently undergo calcification, which may ultimately result in an increase in the high-attenuation calcified component of the tumor. The typical progression of a tumor, in response to therapy, is from predominantly intermediate-density tissues to low-attenuation necrotic tissue, and ultimately to high-attenuation calcified tissue (Fig. 1). Quantitative analysis of the progression of tumor tissue composition should be of considerable value in assessing the response to therapy. Improved accuracy in such assessment should help in deciding upon the appropriate timing of surgical resection of the tumor, and even the avoidance of surgery.

Tissue Characterization in CT

When a monoenergetic x-ray beam passes through an object of uniform density, it is attenuated exponentially. The linear attenuation coefficient μ is determined by the physical density and atomic composition of the object. Values of μ have been recorded for various human and animal tissues at various x-ray energies.^{32,33} Because CT attenuation coefficients are dependent on the x-ray energy used, CT units are normalized. The CT unit is defined as³⁴

$$\text{CT number} = a \frac{\mu - \mu_w}{\mu_w} \quad (1)$$

where μ_w is the attenuation coefficient of water. When $a = 1,000$, the CT number is in HU.³⁵ Table 1 shows the mean and standard deviation (SD) of the CT values in HU for various tissues and structures in the abdomen.

In this study, HU values of voxels form an integral and significant basis for the algorithms. Many of the imposed restrictions of the segmentation strategy are directly dependent on the expected HU value of the specific organ or tissue being segmented.

Table 1. Mean and standard deviation (SD) of CT values in Hounsfield units (HU) for several types of abdominal tissue

Tissue	CT value (HU)	
	Mean	SD
Air ^a	−1,006	2
Fat ^a	−90	18
Skin ^b	+16	11
Spinal canal ^b	+23	15
Kidney ^a	+32	10
Muscle ^a	+44	14
Necrosis ^a	+45	15
Viable tumor ^a	+91	25
Bone marrow ^a	+142	48
Calcification ^a	+345	155
Bone ^a	+1,005	103

^aObtained from Ayres et al.²⁷

^bEstimated from the CT exams with contrast used in the present study, based on approximately 1,000 voxels in each category. Because of the contrast medium, CT values of vascularized tissues are expected to increase by 30–40 HU.

Need for Fuzzy Segmentation

Segmentation of the tumor in neuroblastoma is complicated by the fact that the mass is almost always heterogeneous in nature; furthermore, viable tumor, necrosis, calcification, and normal tissue are often intermixed (see Fig. 1). Commonly used segmentation algorithms, such as thresholding and region growing, employ the all-or-nothing assignment technique. This approach works well when there is clear object definition. To accommodate the heterogeneity of organs and neuroblastic tumors, the inherent variability of biological systems, and overlapping regions of interest in medical images, the rigid parameters of segmentation algorithms need to become flexible. In addition, the elements of human intuition that make manual segmentation possible should be incorporated into segmentation methods. The computational representation of imprecise, vague, and ambiguous parameters has become possible with the advent of segmentation techniques based on fuzzy sets.^{36,37}

With the view to capture the sense of the graded composition of objects in CT volumes and their connectedness, Udupa and Samarasekera³⁸ described efficient algorithms for extracting fuzzy connected objects from membership data. This method facilitates the separation of objects that have similar image intensity properties but are

located in different spatial regions. Fuzzy connectedness provides the parameters flexibility and eases the algorithms from strict requirements.

The fuzzy connectivity method of Udupa and Samarasekera³⁸ has been successfully applied for the segmentation of a few types of tumors. Moonis et al.³⁹ used a semiautomated segmentation technique based on fuzzy connectivity for the estimation of tumor volume in MR images of the brain. The method requires the manual selection of multiple representative points (seed voxels) within the tumor. The tumor is segmented using the specified seed voxels and the fuzzy connectivity algorithm. Extraneous regions, such as the scalp and the orbit, were removed by editing the results of segmentation, as necessary. The authors reported that the segmented tumor volumes were highly reproducible in the absence of editing, with intraobserver coefficients of variation in the range 0.15–0.37% for gadolinium-enhanced volumes and 0.29–0.38% for axial fluid-attenuated inversion recovery (FLAIR) volumes. It was also observed that editing produced smaller volumes, with a coefficient of variation in the range 0.2–1.3%.

Udupa et al.⁴⁰ developed a system for the segmentation and volume estimation of multiple sclerosis lesions. A fuzzy connectivity algorithm was applied to the segmentation of the white matter, gray matter, and cerebrospinal fluid (CSF) in the brain, based on seed points manually provided by the operator. The volumetric spaces present between the segmented white matter, gray matter, and CSF were considered as potential lesion sites, and presented to the operator for acceptance or rejection. The method was reported by the authors as being highly reliable and consistent, with a coefficient of variation in the measured volume of 0.9%, and a mean false-negative volume fraction of 1.3%.

Hata et al.⁴¹ used a fuzzy connectedness method to perform intraoperative segmentation of glioma in MR images. The technique requires the manual selection of representative points in the tumor to guide the fuzzy connectedness algorithm. Quantitative comparison was made between the result of segmentation and the tumor as delineated by a radiologist. The result of segmentation was considered to be good, with an average similarity coefficient of 0.80 and an average match of 76%.

METHODS FOR SEGMENTATION OF THE NEUROBLASTIC TUMOR

Fuzzy Connectivity

Let X be a reference set, and let x be an element of X . A *fuzzy subset* of X is a set of ordered pairs

$$A = \{(x, \mu_A(x)) | x \in X\}, \quad (2)$$

where

$$\mu_A : X \mapsto [0, 1] \quad (3)$$

is the *membership function* of A in X .⁴²

Consider two sets X and Y ; let x designate an element of X and let y designate an element of Y . The set of ordered pairs (x, y) defines the product set $X \times Y$.⁴² A *fuzzy relation* ρ in X is a fuzzy subset of $X \times X$, defined as³⁸

$$\rho = \{((x, y), \mu_\rho(x, y)) | (x, y) \in X \times X\}, \quad (4)$$

where

$$\mu_\rho : X \times X \mapsto [0, 1] \quad (5)$$

Let S represent a set of features for each volume element or voxel, consisting of the spatial location and other local properties, such as CT value and local curvature. A fuzzy relation $\eta: S \times S \mapsto [0, 1]$ is called *fuzzy affinity*.³⁸ The affinity relation $\eta(a, b)$ between two voxels a and b should have the following properties: $\eta(a, a) = 1$ (the relation is reflexive) and $\eta(a, b) = \eta(b, a)$ (the relation is symmetric). Although there are no theoretical restrictions on the definition of fuzzy affinity, computational reasons demand some limitations. In practice, affinity should be dependent on the degree of spatial adjacency of the voxels considered as well as the similarities between their HU values: the closer the voxels and the more similar their values, the greater the affinity.

A path of size m between two voxels a and b is a sequence $\langle c_1, c_2, \dots, c_m \rangle$, $m \geq 2$, of voxels c_i , such that $c_1 = a$ and $c_m = b$. The strength assigned to a path is $\min_{1 \leq i < m} \{\eta(c_i, c_{i+1})\}$. The connectedness of two voxels c and d is dependent on all possible connecting paths between the two voxels. A connecting path is formed by a sequence of links between successive adjacent voxels in the path. The strength of each link is the affinity between the adjacent voxels in the link; the strength of a path is the strength of its weakest link. Finally, the strength of fuzzy connectedness between two voxels a and b is the strength of the strongest path.

To extract and define a fuzzy object from a CT volume, a seed voxel is needed to initialize the fuzzy connectivity algorithm. The seed voxel is assigned the maximum membership of one. The region is grown by evaluating the connectedness between each voxel in the CT volume and the seed voxel, where each voxel is assigned the value of the affinity of the weakest link of the strongest path to the seed voxel. This procedure produces a membership volume. To obtain hard binary segmentation, if desired, the membership volume may be thresholded at an appropriate strength of connectedness.

In our work, $\eta(a, b) = 0$ if voxels a and b are not six-connected neighbors (within a $3 \times 3 \times 3$ block), and

$$\eta(a, b) = \exp \left\{ -\frac{1}{2} \left[\frac{\left(\frac{f(a) + f(b)}{2} \right) - \mu}{\sigma} \right]^2 \right\}, \quad (6)$$

if a and b are neighbors, where $f(a)$ is the value of voxel a in HU, $f(b)$ is the value of voxel b in HU, and μ and σ are the

mean and SD of the region in HU. For segmentation of neuroblastic tumors, the values of μ and σ were automatically calculated from a fixed region surrounding the manually selected seed voxel.

Effects of Leakage and Interfering Structures

In our initial experiments,^{43,44} the fuzzy connectivity algorithm was observed to perform well with tumors including

Fig 2. (a) Manual segmentation (black line) of a calcified tumor mass in one CT slice of a 2-year-old male patient. Note that the tumor has metastasized, as indicated by the two additional segmented regions, located immediately above the vertebra. (b) The same slice as (a) of the fuzzy connectedness membership volume obtained by 3D region growing for the tumor region illustrated in (a) with $\mu = +361$ HU and $\sigma = 55$ HU. (c) Slice view of the thresholded version of the membership volume in (b) at threshold = 0.80. (d) Slice view of the thresholded volume morphologically closed using an elliptical structuring element of size $1.85 \times 1.85 \times 5$ mm. All images were processed in 3D volume datasets. Representative 2D slices are used in the figures to illustrate fine details as required. See Figure 3 for 3D views of the segmented tumor.

Fig 3. (a) Bone volume and the primary tumor mass segmented by the proposed algorithm. (b) Tumor volume segmented by the radiologist (G.S. Boag). The radiologist identified multiple secondary tumor regions; however, only the primary tumor was considered in the segmentation procedure. The bone volume segmented automatically by image processing is shown for reference. See Figure 2 for detailed illustrations of a single slice of the CT volume.

significant portions of dense calcifications (Fig. 2b). Regardless, further morphological processes⁴⁵ were necessary to obtain improved volumetric estimates. Figure 2(c) is the result of thresholding the membership volume in Figure 2(b). Although the tumor is predominantly calcified, some necrosis is still present. The necrotic areas are represented by the holes in Figure 2(c). A high-valued mean was used in the fuzzy connectivity algorithm, for this case, to reflect the large proportion of calcification. As a result, significantly lower valued necrotic tissue is included with low membership. The holes were morphologically closed to allow for better tumor definition (see Fig. 2d). Figure 3(a) shows the resulting tumor definition in 3D and the bone structure for reference. Figure 3(b) shows the 3D tumor volume segmented by the radiologist (G.S. Boag). The radiologist has identified multiple secondary tumor regions; however, only the primary tumor was considered in the segmentation procedure.

When the fuzzy connectivity algorithm was applied to diffuse, heterogeneous masses, the resulting tumor definition was poor (Fig. 4b). This is attributable to the fact that diffuse, heterogeneous masses have large variations in HU values. The large σ or SD required in Equation (6) causes spatially connected objects of dissimilar HU values to be included in the segmented tumor volume. The fuzzy region grown for the tumor in Figure 4(b) most notably leaks through the mesentery into the peripheral muscle (abdominal wall and the paraspinal

muscles). In addition, the fuzzy region grown also leaks through the mesentery, retroperitoneal muscles, and the sacral region of the vertebral column into the vertebral foramina and the spinal canal.

Segmenting known structures based upon knowledge of their shape, location, HU value, and radiological characteristics, and then removing them from the CT data could limit the scope of growth of the fuzzy connectivity algorithm, and help to improve tumor definition.⁴⁶ To segment the known structures, some landmarks for location are required. Because all CT volumes include air that is external to the body, it is advantageous to begin landmarking from the outer limits of the image. The spinal column is an important landmark for several purposes.⁴⁷ Segmentation and subsequent removal of the known layers and organs allows for constant reference, and could facilitate the removal of the surrounding, interfering structures.

Removal of External Artifacts, Peripheral Muscle, and Spinal Canal

In our procedure to obtain the peripheral muscle, the surrounding external air, external artifacts, and the skin and peripheral fat are segmented and removed. Once these organs and structures are removed, the peripheral muscle is exposed

Fig 4. (a) Manual segmentation (black line) of a diffuse, heterogeneous tumor mass in one CT slice of a 2-year-old female patient. (b) The same slice as (a) of the fuzzy connectedness membership volume obtained by 3D region growing for the tumor. (c) The same slice as (a) of the fuzzy connectedness membership volume obtained by 3D region growing for the tumor, after the surrounding air, skin, peripheral fat, peripheral muscle, and spinal canal were removed from the original CT image by separate 3D segmentation procedures. (d) Slice view of the thresholded volume of the membership volume in (c) at 0.80 after morphological closing. The fuzzy connectivity in (b) and (c) was computed by using $\mu = +57$ HU and $\sigma = 22$ HU.

and easily delineated. The spinal canal is removed by using the bone structure as reference.⁴⁷ Such removal of connected structures with known HU values reduces the image volume, and limits the potential for leakage of the tumor volume during segmentation. The strategy described above is summarized in the flowchart in Figure 5, and described in detail below.

Air, by definition, has a CT value of $-1,000$ HU. Skin has a mean CT value of $+16$ HU with $SD = 11$ HU, based on

estimations from CT exams by obtaining manually segmented regions of skin with approximately 500 voxels in each region (Table 1). A simple region-growing procedure with the voxel at $(0, 0, 0)$ being the seed voxel and a thresholding range of $-1,100$ to 5 HU could produce the outer boundary of the skin. The value of $-1,100$ HU was chosen to account for potential noise. Note that this region external to the patient could include clothing, blankets, pillows, and tubes connected to intravenous

Fig 5. Flowchart of the strategy for segmentation of the neuroblastic tumor.

drips. The HU values of cloth items are lower than that of skin and do not constrain the region-growing procedure. Although the intravenous drip with contrast is external to the body and has a much higher HU value than that of skin, it does not constrain the air region, as the intravenous drip tube does not

encompass the body. Then, to remove the tube, the air region is morphologically closed using a structuring element of size $3 \times 3 \times 5$ mm.

The usual thickness of skin is 1–3 mm. Using the parameters of skin thickness and the expected HU value plus

$2 \times \text{SD}$, the outer boundary previously obtained is shrunk by using a 3D morphological operator to include the skin.

The next expected layer is fat. Fat has a mean CT value of -90 HU with $\text{SD} = 18$ HU (Table 1). The thickness of fat varies significantly from one individual to another. The thickness of fat may be manually estimated from each CT exam. The skin boundary is then morphologically eroded to include the fat layer.

The process is then repeated to include the peripheral muscle. The anatomical structures of skin and peripheral fat were not observed to interfere in the scope of growth of the fuzzy connectivity algorithm for tumors; however, their segmentation and removal provides the easiest route to the peripheral muscle, a structure that was observed to become mixed with the fuzzy segmented tumor volume. Muscle has a mean CT value of $+44$ HU with $\text{SD} = 14$ HU (Table 1). The thickness of muscle is manually estimated from the CT exams in the present work. The resulting combined volume of the surrounding air, skin, peripheral fat, and peripheral muscle is assigned an arbitrarily high value greater than that of bone to ensure that further application of the fuzzy connectivity algorithm will not include the peripheral muscle.

The fuzzy connectivity algorithm may be successfully applied to structures that do not have much variability in HU values; the spinal canal is one such structure that was observed to interfere with tumor segmentation (Fig. 4b). The spinal canal was automatically segmented⁴⁷ by using the Hough transform for the detection of circles and fuzzy connectivity, and the region was assigned an arbitrarily high value.

RESULTS OF SEGMENTATION OF THE NEUROBLASTIC TUMOR

The proposed methods for segmentation were applied to 10 contrast-enhanced CT exams of four patients, aged 2 weeks to 11 years. All of the CT exams were obtained with a helical CT scanner (GE Medical Systems Lightspeed QX/i) at the Alberta Children's Hospital (Calgary, Alberta, Canada), with an interslice resolution of 5 mm and intraslice resolution varying from 0.35 to 0.55 mm. Approval was obtained from the Conjoint Health Research Ethics Board, Office of Medical Bioethics, University of Calgary, and Calgary Health Region.

The result of the application of the fuzzy connectivity algorithm to segment a highly calcified tumor is shown in Figure 2b. The algorithm performed well because the average tumor tissue density is high with respect to the densities of the adjacent structures. To view the results of the segmentation algorithm in 3D, a volume rendering software (AVS Express) was used. Figure 3a shows the 3D segmentation result of the algorithm (see Fig. 2d for a slice view). Figure 3(b) shows the 3D manual segmentation of the same exam

(see Fig. 2a for reference). Note the presence of secondary tumoral regions; however, this study was focused on the segmentation of the primary tumor mass only.

When the fuzzy connectivity algorithm was applied on its own to diffuse, heterogeneous tumors, the result of segmentation, was poor, as shown in Figure 4(b). The similar density values and close proximity of the tumor voxels and the surrounding soft-tissue voxels caused the results of segmentation to leak. The segmented region most notably leaked through the mesentery into the neighboring peripheral muscles. In addition, because the region was grown in 3D, it leaked into the vertebral foramina and the spinal canal through the lower abdomen and the sacral region of the vertebral column. The CT volume related to Figure 4(a) was subjected to the procedure outlined in Removal of External Artifacts, Peripheral Muscle, and Spinal Canal for the removal of selected tissues and organs prior to segmentation of the tumor, and the results are shown in Figure 4(c). It is seen that the erroneous inclusion of the spinal canal and peripheral muscle (seen in Fig. 4b) has been obviated by their prior identification and removal. Figure 4(d) shows the volume in Figure 4(c) after thresholding at 0.80 and morphological closing using an elliptical structuring element of size $2.87 \times 2.87 \times 5$ mm. Note that regions smaller than the structuring element have been removed from the tumor definition. A larger structuring element may be chosen to fill the holes remaining in the result. However, a larger structuring element may cause the removal of parts of the tumor during the erosion process of the closing operation.

The result of application of the fuzzy connectivity algorithm to a diffuse and calcified tumor is shown in Figure 6(b), with the parameters $\mu = +154$ HU and $\sigma = 98$ HU. A large σ is needed in this case to accommodate the HU range of diffuse tumoral tissue to calcified tissue. Figure 6(b) shows the membership volume with the seed voxel in the calcified region. Figure 6(c) shows the membership volume with the seed voxel in the diffuse tumoral tissue region. Figure 6(d) shows a slice of the binary segmented volume obtained from the results shown in Figure 6(b) after thresholding at 0.80 and morphological closing. Fuzzy region growing starting with a low-density tissue voxel resulted in the inclusion of the liver, spleen, heart, and kidneys (Fig. 6c). When the seed voxel was placed in the calcified portion of the tumor,

Fig 6. (a) Manual segmentation (black line) of a diffuse and calcified tumor mass in one CT slice of a 2-year-old male patient. (b) The same slice as (a) of the fuzzy connectedness membership volume obtained by 3D region growing for the tumor region illustrated in (a) with a seed voxel in the calcified region. (c) The same slice as (a) of the fuzzy connectedness membership volume obtained by 3D region growing for the tumor region illustrated in (a) with a seed voxel in the diffuse tumoral tissue region. (d) Slice view of the tumor region after thresholding the membership volume in (b) at 0.80 and morphological closing using a structuring element of size $2.75 \times 2.75 \times 5$ mm. The procedures to obtain the results in (b) and (c) used the same parameters of $\mu = +154$ HU and $\sigma = 98$ HU.

the tumor definition included the left kidney and portions of the contrast-enhanced stomach (in slices other than the slice shown in Fig. 6).

Quantitative Evaluation of the Results of Segmentation

Segmentation results were compared with the manually segmented volume as delineated by a

pediatric radiologist (G.S. Boag). The total error, denoted by ε_T , was calculated as

$$\varepsilon_T = \frac{V(A) - V(R)}{V(R)} \times 100\%, \quad (7)$$

where A is the segmented tumor as determined by the proposed algorithm, R is the primary tumor

mass as determined from the manual segmentation performed by the radiologist, and $V(A)$ and $V(R)$ are the respective volumes of the segmented tumors.

A false-positive (FP) voxel is a voxel that is included in the tumor segmented by the algorithm but not in the manually segmented volume. The FP error, denoted by ε_{FP} , was calculated as

$$\varepsilon_{FP} = \frac{V(A) - V(A \cap R)}{V(R)} \times 100\%. \quad (8)$$

A false-negative (FN) voxel is a voxel that is included in the manual tumor definition but not in the tumor segmented by the algorithm. The FN error, denoted by ε_{FN} , was calculated as

$$\varepsilon_{FN} = \frac{V(R) - V(A \cap R)}{V(R)} \times 100\%. \quad (9)$$

Eight of the segmented tumor volumes had FN error less than 12%; the remaining two cases had an FN error between 20% and 30%. Three cases had an FP error less than 20%, five cases had an FP error between 35% and 50%, and the remaining two cases had an FP error over 50%. High FP error rates were obtained for some cases, but relatively low FN error rates were obtained in most cases. The high FP percentages indicate that the proposed methodology has low specificity in some cases, whereas the relatively low FN percentages indicate high sensitivity in most cases. The sensitivity represents the capability of the algorithm to recognize tumoral tissue, whereas specificity indicates the accuracy of the algorithm in identifying normal tissue.

DISCUSSION

Segmentation of medical images, in general, and in the specific application to the tumor in neuroblastoma, remains a difficult problem. Relaxing the rigid parameters of traditional segmentation algorithms appears to be a good approach to address this problem. The fuzzy connectivity method of Udupa and Samarasekera³⁸ has been successfully applied for the segmentation of a few types of tumors (see Need for Fuzzy Segmentation for a brief review). The 3D fuzzy connectivity algorithm used in this work provided satisfactory results with tumors that were highly calcified or relatively homogeneous. When the 3D fuzzy connectivity algorithm was

applied to diffuse and heterogeneous tumors, it performed poorly. However, the results were significantly improved with the proposed strategy of prior segmentation and removal of potentially interfering structures.

The 3D fuzzy connectivity algorithm can be adapted to include multiple seeds instead of a single seed voxel.⁴⁸ The use of multiple seeds permits the growth of multiple fuzzy connectedness membership volumes, which could be jointly analyzed or fused³⁷ to obtain improved tumor definition. Also, the seeds may be placed in different regions within the tumor (viable tumor, necrosis, and calcification), and the volumes grown from each seed subsequently merged after thresholding.

Atlas-based techniques may be investigated to help refine the segmentation procedure.⁴⁹ Some work has been conducted in attempts to define automatically the boundaries of normal anatomical structures and subsequently to identify focal or diffuse abnormalities within those organs.⁵⁰ However, neuroblastoma is a disease affecting children, and most of the available atlases use adult proportions. In addition, the neuroblastic tumor may cause deformation of the expected shape and size of neighboring organs. The use and effectiveness of deformable models⁵¹ is being explored. Expected shape and volume properties, as well as compactness measures, could be included in the algorithm to obtain more robust and accurate results.^{48,52} We are working on the development of an interactive tool to permit the user to modify and refine the results of initial segmentation.

Our algorithms have been implemented by using the C programming language. Typical computation times were between 20 and 40 min per case, depending on the volume of the CT data. (Manual segmentation of the tumors by the radiologist took a comparable amount of time.) All experiments were performed on a Dell Precision work station (two Intel Xeon 1.7 GHz processors with 4 GB RAM). Although the work station is capable of parallel processing by using its two processors, the code was not developed to take advantage of this possibility. Yet, it is possible to reduce the execution time of our algorithms by using parallel processing techniques or grid computing. In addition, the fuzzy connectivity algorithm may be replaced by the opening-by-reconstruction algorithm, a faster mathematical morphology method.^{48,52} Bloch⁵³ demonstrated that the opening-by-reconstruction method is

equivalent to the fuzzy connectivity definition of Rosenfeld,⁵⁴ which is a particular case of the fuzzy connectivity method of Udupa and Samarasekera.³⁸ Our initial studies^{48,52} indicate that tumor segmentation may be achieved, on the average, in about 1 min, using opening-by-reconstruction. Regardless, although computer-aided segmentation of tumor volumes, at present, may not improve the time to diagnosis, it has potential use in assessing serial tumor volumes and response to treatment. In consideration of cost-effective workflow, computer-aided segmentation could be initiated by a technologist under the supervision of a radiologist. Ultimately, if such a system were able to identify abnormalities without human intervention, it could possibly reduce the time to diagnosis.

Once segmentation of the tumor mass has been accomplished, the tissue content of the mass may be estimated via statistical modeling and analysis.²⁷ We intend to combine methods for improved segmentation of the tumor mass with procedures for statistical analysis of the tissue composition of the tumor. Quantitative analysis of the progression of tumor tissue composition should be of considerable value in assessing the response to therapy. Improved accuracy in such assessment should help in deciding upon the appropriate timing of surgical resection of the tumor, and even the avoidance of surgery.

Our plans for future work include the development of a web-based resource with a repository of clinical cases, image-based examinations via an architecture for distributed databases in work station clusters, treatment protocols, and related information. The set-up will be designed to provide tools for active maintenance of records of treatment protocols in current application to patients; image processing methods for segmentation and analysis of tumors; access to high-performance computing facilities for multimedia medical information analysis; tools for data mining and statistical analysis; and utilities for computer-supported collaborative work for medical diagnosis.

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