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ABSTRACT

Segmentation of three-dimensional (3D) medical images using deep learning is a challenging task due to the lack of a 3D medical image dataset and their ground truth, resource memory limitations, and imbalanced dataset problem. In this paper, we propose advanced deep learning network for segmentation of 3D medical images. The proposed Multi-projection Network can preserve resource memory by applying two-dimensional (2D) kernels while still obtaining the 3D information from the image by incorporating slices from different planar projections of the 3D image to achieve good segmentation results. The proposed network uses a weighted cost function to address the imbalanced dataset problem and introduces an adaptive weight that considers the probability of each class in the image. The experimental results showed that the proposed Multi-projection Network can produce the highest sensitivity (true positive rate) compared to other architectures despite the high class imbalance in the dataset and small amount of training data.

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1. Introduction

Due to the advanced development of medical technology, three-dimensional (3D) image acquisition methods, such as computed tomography (CT) scanning and magnetic resonance imaging (MRI), are commonly used. This advancement has led to the need for more accurate and efficient 3D image segmentation methods. By performing image segmentation, important objects in the medical image can be recognized and further analysis can be done to extract relevant information about the object and decisions regarding the patient can be made. Many computer-aided methods for medical image segmentation have been proposed. These methods can be divided into threshold-based, region-based, texture-based, model-based, atlas-based, and artificial neural network-based approaches [1–3]. Recent studies have shown that deep learning techniques, such as convolutional neural network (CNN), are useful in medical image segmentation because they can provide high segmentation accuracy [4–11]. Instead of extracting features man-

ually, deep learning can find informative and distinctive features that represent the data using a learning process [9]. Hence, the burden of finding the right features to perform image segmentation or classification shifts from humans to computers [12].

The lack of medical image datasets and their ground truth is a problem when using deep learning for medical image segmentation because this approach requires a large-scale dataset for training to produce good segmentation results [12–14]. Moreover, segmentation of 3D medical images is challenging due to the relations between the three dimensions: ignoring any of these relations will result in information loss. Hence, the most common deep learning approaches, which use two-dimensional (2D) kernels, are not the most suitable methods for the segmentation of 3D medical images. Deep learning approaches that use 3D kernels directly generate large feature vectors, therefore their implementation has high computational cost (resource memory limitations and long training time) [15]. Moreover, because networks that use 3D kernels use 3D images or 3D image patches as the input data, they are also limited by the number of 3D images in the dataset [13,16].

Another challenge in the segmentation of 3D medical images is the high class imbalance in 3D medical image datasets [8]. Not

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every image contains a segmentation object and when there is an object in the image, the size of the object region tends to be much smaller than the background region. Deep learning algorithms tend to prefer the majority class and suppress the minority class to minimize the network cost, even though the minority class is the one of interest. If this problem is not addressed, the segmentation result of 3D medical images using deep learning will have low sensitivity (true positive rate). Several researches have proposed solutions for this problem by introducing a weight into the cost function of the network [17–19]. Although these methods are effective for binary classification problems using deep learning, it is difficult to calibrate the proposed functions for multiclass classification problems.

In this paper, we propose an advanced deep learning network for segmentation of 3D medical images. The proposed architecture, called Multi-projection Network, preserve resources' memory by applying 2D kernels while still obtain the 3D information of the image by incorporating slices from different planar projections of the 3D image to achieve a good segmentation result. We also introduce an adaptive weighted cost function for the network to address the imbalanced dataset problem in 3D medical image segmentation. This weight is calculated by considering the probability of each class in the image batch. The proposed cost function improves the network's performance in detecting the minority class and can be also used for multiclass segmentation. Three kinds of datasets were used in an experiment to represent the problems of 3D medical image segmentation, such as the imbalanced dataset problem and a limited amount of available training data. This paper also provides a comparison of the proposed method with several other network architectures to analyze the accuracy of the proposed network for binary segmentation of one-modality 3D medical images.

2. Related works

Image segmentation classifies each pixel in the image individually. CNN can be used for image segmentation by using image patches to determine the class of a pixel. The drawback of this approach is that input patches from neighboring pixels overlap so that the same convolutions are computed many times over [20]. Fully Convolutional Network (FCN) substitutes the fully connected layer in CNN with a convolution layer [21]. Using FCN, the network can take an entire image as the input and produce an entire image as the output, thus speeding up the computation process. However, FCN approaches for medical image segmentation do not have an adequate spatial resolution in their direct output label space [22]. To solve this problem, a modified version of FCN, called U-Net [5] has been proposed. U-Net and its variations are among the most well known deep learning methods for medical image segmentation [20]. It has a similar architecture as Autoencoder, a symmetrical neural network that learns the features of the dataset in an unsupervised manner [23]. It combines an equal number of layers and processes on the encoder and decoder side. The difference between Autoencoder and U-Net is that U-Net uses skip connections that bypass information from the encoder layers to the decoder layers to help recover the full spatial resolution at the network's output [24]. U-Net can take an entire image as input and give the segmentation map directly as output, therefore it can take into account the global information of the image.

Several researches have been conducted for 3D medical image segmentation using a number of different approaches. The first approach is to treat the 3D images as a set of 2D slices and applying a 2D deep learning strategy to segment the images [4,7,8,25,26]. Although this approach generates more training data for the network, it dismisses the connection between consecutive slices in the 3D image. Several researches examined this problem by adding a

post-processing step, such as using 3D Conditional Random Field, to obtain the inter-slice information [25]. Another approach for 3D medical image segmentation is by adding the image depth in the deep learning process [6,18,27,28]. Voxels are used instead of pixels, therefore 2D convolution and 2D pooling will be substituted by 3D convolution and 3D pooling. Although this approach is the most obvious way to preserve the inter-slice information, it is limited by the small size of the 3D dataset and the resource memory.

Several researches have attempted to use a 2D deep learning strategy while preserving the inter-slice information by integrating several 2D projections from different points of view of the 3D image in a network. For 3D medical images, this is done by dividing the 3D image into three different planes (x, y, and z) and creating three different sets of 2D slices [29–31]. Prasan, et al. [29] adopted this approach in a method called Triplanar Convolutional Neural Network on knee cartilage segmentation images. The 3D image patches consisting of voxels are extracted from the image and then divided into three different sets of 2D slices. Each set of slices will become the input for a CNN. The outputs of the three CNNs are concatenated to obtain a joint output, which will be fed into the softmax classifier to obtain the classification result of each voxel.

3. Material and methods

3.1. Dataset

We used three datasets in our experiments. The first dataset used was BRATS-2012 [32,33], a dataset of brain images for brain tumor segmentation that was acquired using MRI (Magnetic Resonance Imaging) scanning. There are 80 brain images in the dataset, consisting of multi-contrast MR scans of 10 low-grade and 20 high-grade glioma patients and simulated images of 25 low-grade and 25 high-grade glioma subjects. The size of the 3D images in this dataset vary. The second dataset used was BRATS-2018, the latest version of the BRATS dataset. It consists of the BRATS-2012 and BRATS-2013 datasets, manually annotated and revised by clinical experts. This dataset consists of 285 MRI scans divided into 210 high-grade glioma subjects and 75 low-grade glioma subjects. Each MRI scan consists of 155 2D images with a size of 240×240 pixels.

There are four modalities for each brain image in the BRATS dataset, namely T1 (native), T1C (post-contrast T1-weighted), T2 (T2-weighted), and Flair (T2 Fluid Attenuated Inversion Recovery). The ground truth provided four segmentation labels, namely non-tumor, edema, necrosis, and enhanced structures. We treated the segmentation problem using BRATS dataset as a binary segmentation problem in which the segmentation object was the whole brain tumor. This included edema, necrosis and enhanced structures. Hence in our research there were only two classes in the BRATS-2012 and BRATS-2018 datasets, i.e. whole brain tumor and non-tumor. We used only one modality for the input of the network, i.e. the T1C modality that is better at showing brain tumors than other modalities.

The third dataset used was CBCT (Cone-Beam Computed Tomography) containing scans of human jaws. We acquired this scan from the hospital *Rumah Sakit Gigi dan Mulut, Universitas Airlangga (RSGM UNAIR)*, which used an ORTHOPANTOMOGRAPH™ OP300 3D X-ray unit. The field of view (FOV) width and height of the scanner are 79.8 mm and 60 mm, respectively. The dataset consisted of jaw images from 7 patients. The segmentation object was teeth and the manually annotated ground truth was confirmed by radiologist experts. The 3D images had sizes of $266 \times 266 \times 200$ voxels. The 2D images were obtained by slicing the 3D image along the axial plane. To make them uniform, the 2D images in the BRATS-2012, BRATS-2018 and CBCT datasets were resized to 128×128 pixels while only the middle 128 images of each 3D scan

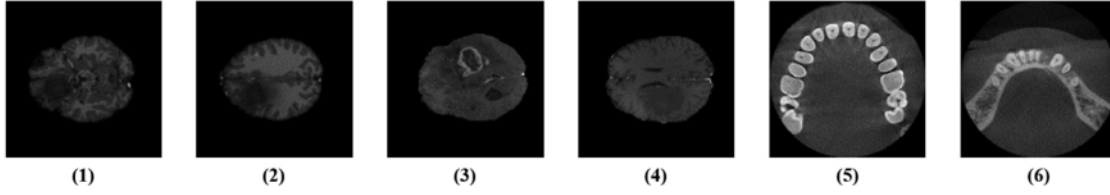


Fig. 2. Input images.

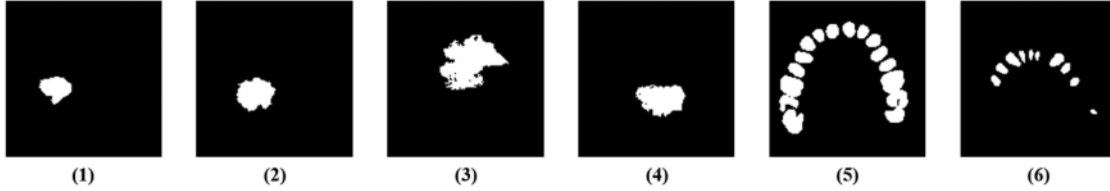


Fig. 3. Target images.

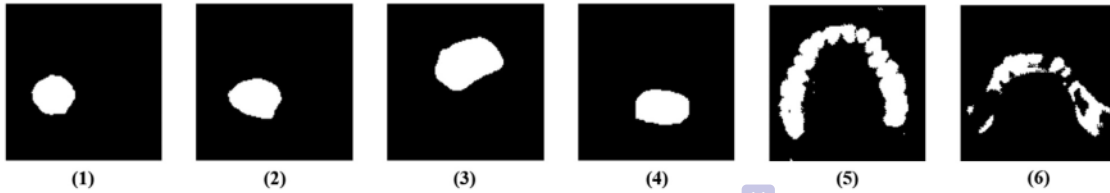


Fig. 4. Segmentation results of Multi-projection network with the proposed weighted cross entropy as the cost function.

weight of the minority class can be achieved by using the probability of majority class as the weight of the minority class. However, using a reversed class probability directly as the weight can make the cost function return zero value when the number of elements of one of the classes is zero, hence each class must have minimal one element. The reverse of the normalized probability function of each class will be $1 - ((n_k + 1)/(N + K))$ where $K = 2$ in a binary segmentation task. This function can be expanded for multiclass segmentation problems as in Eq (3).

$$\text{Weighted RMSE} = \sqrt{\frac{1}{N} \left(\sum_{k=1}^K \frac{1 - \frac{n_k + 1}{N + K}}{K - 1} \sum_{\hat{x}_i \in C_k} (\hat{x}_i - x_i)^2 \right)} \quad (3)$$

However, while the RMSE cost function can be applied to binary classification tasks by rounding or thresholding its value, it is difficult to apply in multiclass classification tasks. A cross-entropy cost function is better suited for classification tasks. The proposed weight can be assigned to the cross-entropy cost function using a similar approach. Let $\hat{y}_k^{(i)}$ be the actual probability of pixel $(\hat{y}^{(i)})$ belonging to class k and $y_k^{(i)}$ be the output probability of pixel $(y^{(i)})$ belonging to class k . The cross-entropy error for binary segmentation is calculated using Eq (4). Using this formula as the cost function will result in the same error value, either when a higher number of false negatives or a higher number of false positives occurs. To make the function prefer the occurrence of false positives over false negatives, a weight w needs to be introduced in the first part of the formula. Using the proposed weight $w = (1 - ((n_k + 1)/(N + K)))/(K - 1)$, the weighted cross-entropy formula will be as in Eq (5).

$$\text{Cross - entropy} = -\frac{1}{N} \sum_{i=1}^N \sum_{k=1}^K \hat{y}_k^{(i)} \log(y_k^{(i)}) \quad (4)$$

$$\text{Weighted Cross - entropy} = -\frac{1}{N} \sum_{i=1}^N \sum_{k=1}^K (w \hat{y}_k^{(i)} \log(y_k^{(i)})) \quad (5)$$

If the proposed cost functions are applied to a neural network that takes batches or mini-batches consisting of several images as input, the weight of each class in the cost function will be calculated for each batch. The weight of the cost function adaptively provides a different value based on the class probability of each batch. Moreover, while the original cost function will give an error value in the range of $[0, 1]$, the proposed cost function will give an error value in the range of $[0, \infty]$ due to its weight.

4. Experimental results

This research was implemented on Python using the Tensorflow library. The specifications of the machine on which network was run were is GPU GTX 1080, RAM 2 x 8GB 2400MHz DDR4. Examples of the input images and their corresponding ground truth (target images) are shown in Figs. 2 and 3, respectively. Examples of the output images from Multi-projection Network using the proposed weighted cost-entropy as the cost function are shown in Fig 4. Image (1) and image (2) are from the BRATS-2012 dataset, image (3) and image (4) are from the BRATS-2018 dataset, and image (5) and image (6) are from the CBCT dataset.

Because of the imbalanced dataset problem, accuracy cannot be the only evaluation metric for measuring the performance of deep learning in 3D medical image segmentation. A high accuracy is not enough to demonstrate the goodness of the evaluated method because in dataset with high class imbalance a method may presents a high accuracy value even though it fails to recognize the area of interest (object) [37]. Therefore, sensitivity (true positive rate) and specificity (true negative rate) were also used to evaluate the performance of the proposed network. The segmentation result is

Table 1
Comparison of deep learning methods on several datasets.

Network	Performance (%)								
	BRATS-2012			BRATS-2018			CBCT		
	Acc	Sen	Spe	Acc	Sen	Spe	Acc	Sen	Spe
Autoencoder [34]	98.30	89.49	98.31	97.84	70.24	98.02	94.66	87.39	94.54
FCN [21]	98.31	91.18	98.30	97.44	68.69	97.63	95.12	89.09	94.91
2D U-Net [5]	98.59	91.03	98.58	97.64	71.34	97.81	95.16	88.41	95.07
3D U-Net [27]	97.90	78.33	98.00	97.32	74.54	97.54	94.31	85.22	94.19
Multi-projection	98.07	93.67	98.06	97.49	74.51	97.62	94.26	90.09	94.07

Table 2
Comparison of cost function on the proposed Multi-projection network.

Cost function	Performance (%)								
	BRATS-2012			BRATS-2018			CBCT		
	Acc	Sen	Spe	Acc	Sen	Spe	Acc	Sen	Spe
RMSE	99.59	58.41	99.88	98.58	2.53	99.98	96.77	74.74	97.91
Cross-entropy (CE)	99.55	67.35	99.77	98.58	0.33	100	96.74	74.90	97.75
Globally-weighted RMSE	98.64	91.09	98.64	98.17	70.62	98.37	94.70	85.19	94.74
Globally-weighted CE	98.66	89.05	98.67	97.72	72.53	97.95	94.63	89.92	94.47
Proposed RMSE	98.68	92.16	98.67	98.19	71.14	98.41	95.21	88.52	95.11
Proposed CE	98.07	93.67	98.06	97.49	74.51	97.62	94.26	90.09	94.07

considered good if it has high accuracy, sensitivity, and specificity. High sensitivity means that the method has good ability to detect the object class, while high specificity means that the method has good ability to detect the background class.

4.1. Data splitting

Each of the datasets was split into a training set and a test set. The BRATS-2012 dataset, consisting of 80 MRI images, was divided into 70 training data and 10 testing data. The BRATS-2018 dataset, consisting of 285 MRI images, was divided into 250 training data and 35 testing data. The CBCT dataset, consisting of 7 images, was divided into 5 training data and 2 testing data. The 3D images from the dataset were randomly assigned for training or testing process. The test set is also used for the validation process. A number of experiments was conducted using k -fold cross validation for the data splitting process but the results were not significantly different from using the training and testing split. Therefore we chose not to use the cross validation method so that the computational cost would not be increased.

4.2. Comparison with other networks

Experiments were conducted to evaluate several network architectures for binary segmentation of 3D medical images. The architectures were: Convolutional Autoencoder [34], FCN [21], 2D U-Net [5], 3D U-Net [27], and the proposed Multi-projection Network. The 3D U-Net has the same network architecture as the 2D U-Net but it uses 3D volumetric image as the input and uses 3D kernels for its process. The size of the image batch for Autoencoder, FCN, and 2D U-Net was set to 128 2D images while the size of the image batch for 3D U-Net and Multi-projection Network was set to 1 3D image (128 2D images). For each training set and architecture, we set 50 as the training epoch because the given training error has reached convergence.

We implemented the architecture and the cost function of the compared methods according to their respective paper. However, their hyper-parameters setting, consist of the number of convolution and pooling layers, kernel size, stride, and number of output channels, are made similar with the proposed Multi-projection Network to provide equivalent comparison. In their respective pa-

per, the compared methods usually use cross-entropy as their cost function and it is mentioned that weight should be used in case of imbalanced dataset. However, the weight is also a hyper-parameter. For this research, the weight value for the cost function of compared methods is set according to the ratio between minority and majority class in each dataset, in which we called as globally-weighted cross-entropy. We train all of the networks from scratch and do not use transfer learning.

Table 1 shows the comparison results for the BRATS-2012, BRATS-2018, and CBCT datasets, respectively. The network's performance was measured using accuracy (Acc), sensitivity (Sen), and specificity (Spe). The performance measurements in Table 1 show that the proposed Multi-projection Network had a higher sensitivity value than Autoencoder, FCN, and 2D U-Net for all datasets. This means that Multi-projection Network can handle the imbalance problem better than the other networks that use 2D kernels. However, 3D U-Net which uses 3D kernels had the highest sensitivity value compared to the other networks for BRATS-2018 dataset. It can be concluded that obtaining the 3D information for segmentation of 3D medical images is crucial to produce an accurate segmentation result in terms of the sensitivity metric. However, the 3D U-Net method had the lowest sensitivity value compared to the other networks for the BRATS-2012 and CBCT datasets. This is because for 3D U-Net, which takes 3D images as input, the BRATS-2012 and CBCT training sets do not contain enough images to make the network perform well.

4.3. Evaluation of cost function

The performance of Multi-projection Network using different cost functions was compared, as shown in Table 2. The compared cost functions are root mean squared error (RMSE), cross-entropy (CE), weighted RMSE using the global probability of each class in the dataset (globally-weighted RMSE), weighted cross-entropy using the global probability of each class in the dataset (globally-weighted CE), RMSE using the proposed weight (proposed RMSE), and cross-entropy using the proposed weight (proposed CE). This experiment was conducted on BRATS-2012, BRATS-2018, and CBCT datasets respectively, as shown in Table 2.

The performance evaluation in Table 2 shows that the use of the proposed weighted cost function produced a higher sensitivity

value, especially on datasets with high class imbalance, such as BRATS-2012 and BRATS-2018. The ratio between minority and majority class in the BRATS-2012, BRATS-2018, and CBCT datasets is 15:1000, 13:1000, and 45:1000, respectively. Higher class imbalance will result in lower sensitivity of non-weighted cost functions. The use of a weighted cost function that considers the class probability in each batch gives Multi-projection Network a slightly better accuracy and sensitivity value than the use of a globally-weighted cost function, which uses the class probability in the dataset directly.

5. Discussion

Although deep learning has many advantages in 3D medical image segmentation, this approach is not always the best method for specific datasets because it has limitations, such as requiring sufficient training data and its inability to deal with imbalanced datasets. The common approach of addressing the imbalanced dataset problem is to balance the dataset by reducing the number of majority class instances in a sample subset or by over-sampling the minority class, including the creation of synthetic samples [38]. However, in this research we preferred to address the imbalanced dataset problem by modifying the network cost function rather than modifying the samples because of the characteristics of the input data that were used. In this research, 3D medical images were used as the input data that consisted of sequential 2D images. This characteristic will make it difficult to reduce the 2D slice images or add 2D synthetic images to the sample subset because it can damage the data sequence. Moreover, creating additional 3D synthetic images as samples is not an option because it does not solve the imbalanced dataset problem because the class imbalance in one 3D medical image for segmentation purpose is already high.

The proposed method was tested on datasets with class imbalance. High class imbalance makes harmful effect on the classification results. A method can be identified as better than others if it performs better on the data with high class imbalance [39]. Adding weight to the cost function of Multi-projection Network can solve the imbalanced dataset problem. By considering the local probability contained in each batch for the cost function's weight, the network's kernels will be updated according to all of the images that are contained in the input batch. Because the 2D slices are inserted sequentially to form the appropriate 3D image, there are input batches that have higher class imbalance than the others which results in higher error rate in some of the batches. After 50 iteration, the error of the training process using cross-entropy as the cost function (without weight) is about 0.07 on BRATS-2018 dataset, meanwhile the error rate of the training process using weighted cross-entropy is about 0.0075. Evaluation of the network's average error or cost rate in each iteration of training process shows that the proposed cost function gives an uneven cost graph due to its adaptive weight. However, this does not pose a problem because the rate of the training cost is globally decreased.

In this research, Multi-projection Network used max pooling for the pooling layer because it leads to faster convergence by selecting superior invariant features, which improves generalization performance [40]. The kernel sizes are important parameters for the convolution layer in deep learning networks. A large kernel size can capture more information from the image than a small kernel size. However, a larger kernel means more computation therefore it leads to higher computational cost and longer training time. In this research we chose to use 3 as the kernel size for all the convolution processes. The selection of a small kernel size is also done by many state-of-the-art deep learning methods to keep both computation and number of parameters contained [41]. Stride = 1 is usually used for the convolution process. However,

in this research there are convolution layers that use stride = 2 to save the resource's space and speed-up the computational time. Multi-projection Network uses Rectifier Linear Unit (ReLU) activation function because it increases the network sparsity and makes the network learn faster [42–45].

The architecture of Multi-projection Network can be further developed for segmentation of 3D objects, where the encoders are used for 2D projections of the 3D object from different sides. However, because the number of encoders depends on the number of projections that are used, it is necessary to consider a training strategy that can reduce the dimensionality of the feature maps. The proposed Multi-projection Network method with its cost function showed promising results for binary segmentation of 3D medical images. However, many aspects can still be investigated and improved in future work. Further research regarding deep learning network parameters, such as effective mini-batch size and number of network layers related to the type of input data and the task of the network, needs to be conducted.

6. Conclusion

In this paper we proposed an advanced network architecture and a cost function for segmentation of 3D medical images. The proposed Multi-projection Network method can preserve resource memory by applying 2D kernels while still obtaining the 3D information from the image by incorporating a number of slices of the 3D image to achieve a good segmentation result. The proposed network's cost function addresses the imbalanced dataset problem by introducing an adaptive weight to the network cost function, which considers the probability of each class in the image. The proposed cost function improves the network's performance in detecting the minority class and can also be used for multiclass segmentation. It had accuracy, sensitivity, and specificity of 97.49%, 74.51%, and 97.62%, respectively, on the BRATS-2018 dataset, which has high class imbalance. Furthermore, the method for assigning adaptive class weight can also be applied to other network cost functions.

The experimental results showed that the proposed Multi-projection Network can reduce the effect of the imbalanced dataset problem and had the highest sensitivity value among the compared network architectures, i.e. Autoencoder, FCN (Fully Convolutional Network), 2D U-Net, and 3D U-Net, on the BRATS-2012 and CBCT datasets. Multi-projection Network had a slightly lower sensitivity value than 3D U-Net on the BRATS-2018 dataset, which confirms the importance of 3D information in segmentation of 3D medical images. Multi-projection Network had accuracy, sensitivity, and specificity of 94.26%, 90.09%, and 94.07%, respectively, on CBCT dataset that consists of 7 3D images. This proves that despite the small amount of training data, the proposed method can have excellent performance on segmentation of 3D medical images. The experimental results showed that the proposed method has the potential to be used and further developed in conducting 3D image analysis and other medical applications, such as brain cancer detection and oral surgery.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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