KSÜ Mühendislik Bilimleri Dergisi, 27(3), 2024
Araştırma Makalesi

KSU J Eng Sci, 27(3), 2024
Research Article

Kahramanmaras Sutcu Imam University
Journal of Engineering Sciences

Geliş Tarihi : 19.01.2024
Kabul Tarihi :02.05.2024

Received Date : 19.01.2024
Accepted Date : 02.05.2024

3-DIMENSIONAL AUTOMATIC SEGMENTATION OF PITUARITY TUMOR USING DEEP LEARNING

DERİN ÖĞRENME KULLANILARAK HİPOFİZ TÜMÖRÜNÜN 3 BOYUTLU OTOMATİK BÖLÜTLENMESİ

Sinan ALTUN[1] (ORCID: 0000-0002-2356-0460)

[1] Kahramanmaraş İstiklal Üniversitesi, Yapı İşleri ve Teknik Daire Başkanlığı, Kahramanmaraş, Türkiye

*Sorumlu Yazar / Corresponding Author: Sinan ALTUN, s.altun@yaani.com

ABSTRACT

The development of a benign pituitary tumor progresses very slowly. Due to this slow development, it may take time to diagnose the patient. The Tumor that will form in the Pituitary Gland, which is effective in the secretion of many hormones and located behind the optic nerves, may cover 2/3 of the Pituitary Gland. In people for whom hormonal balance is essential, due to Pituitary Tumor, Cushing's syndrome diseases can be seen as a result of irregular menstruation, visual disturbances, headache, imbalance in breast milk production, and excess ACTH production. Excess ACTH can lead to excessive weight gain, the appearance of fragile bone structure, skin scars, and emotional changes. The Pituitary Tumor is located in the deepest part of the brain, and it is tough to perform a surgical operation there. Semantic segmentation using deep learning techniques can be successful. With our study, automatic segmentation of the Tumor with an IoU score of up to 98% was possible. This success is relatively high, and promises hope for the CAD system to be created for Pulmonary tumors. The 3D-Unet technique developed recently, can perform automatic segmentation in 3 dimensions. This study aims to automatically segment a Pituitary Tumor, which requires a complex operation, with the 3D-Unet model.

Keywords: Pituitary tumor, hormonal diseases, semantic segmentation, 3D-UNet, deep learning

ÖZET

İyi huylu bir hipofiz tümörünün gelişimi çok yavaş ilerler. Bu yavaş gelişme nedeniyle hastaya tanı konulması zaman alabilir. Birçok hormonun salgılanmasında etkili olan ve görme sinirlerinin arkasında yer alan Hipofiz Bezinde oluşacak tümör, Hipofiz Bezinin 2/3'ünü kaplayabilir. Tümörün büyümesine bağlı olarak sinirler üzerindeki baskı arttıkça bazı belirtiler ortaya çıkar. Hormonal dengenin önemli olduğu kişilerde Hipofiz Tümörü nedeniyle adet düzensizliği, görme bozuklukları, baş ağrısı, anne sütü üretiminde dengesizlik, ACTH fazla üretimi sonucu Cushing sendromu hastalıkları görülebilmektedir. Aşırı ACTH aşırı kilo alımına, kırılgan kemik yapısının ortaya çıkmasına, ciltte yara izlerine ve duygusal değişikliklere neden olabilir. Hipofiz Tümörü beynin en derin kısmında yer alır ve burada cerrahi operasyon yapılması zordur. Derin öğrenme tekniklerini kullanan anlamsal bölümleme başarılı olabilir. Çalışmamız ile Tümörün %98'e varan IoU skoruyla otomatik segmentasyonu mümkün oldu. Bu başarı nispeten yüksektir ve Akciğer tümörleri için oluşturulacak CAD sistemi için umut vaat etmektedir. Son zamanlarda geliştirilen 3D-Unet tekniği, 3 boyutlu otomatik segmentasyon yapabilmektedir. Bu çalışma, karmaşık bir operasyon gerektiren Hipofiz Tümörünün 3D-Unet modeli ile otomatik olarak segmentasyonunu amaçlamaktadır.

Anahtar Kelimeler: Hipofiz tümörü, hormonal hastalıklar, semantik bölütleme, 3B-Unet, derin öğrenme

ToCite: ALTUN, S., (2024). 3-DIMENSIONAL AUTOMATIC SEGMENTATION OF PITUARITY TUMOR USING DEEP LEARNING. *Kahramanmaraş Sütçü İmam Üniversitesi Mühendislik Bilimleri Dergisi*, 27(3), 780-791.

INTRODUCTION

Hormonal structure is one of the critical systems for the human body to perform its duties healthily. Thanks to hormones, the body works in a precise balance and order. The essential organ of this structure is the pituitary gland, which regulates the secretion of hormones while secreting many hormones and ensures that they work effectively (Simander et al., 2023; Geer, 2023). The pituitary gland is in the middle of the lower part of the brain, between the nasal root and the base of the brain, the optic chiasm and optic nerves, where the optic nerves meet in the upper part, the thalamus, which is called the brain of the brain, on the upper sides, the carotid arteries, which are two of the three vessels feeding the brain, and the three vessels feeding the brain in the back. Moreover, the brain stem is the respiratory and cardiac control center. Tumor development in this pituitary gland, because it is a secretory gland, and developmental anomalies are joint because it develops from brain palate cells. Depending on these diseases, due to the anatomical structure and neighborhood, vision problems by compressing the optic nerves, problems in cerebral blood supply due to pressure on the carotid vessels, and brain dysfunction due to its enlargement into the brain may develop (Sharma et al., 2023; Ciavarra, 2023). Growth retardation and sexual development problems occur as a result of the incomplete development of hormones due to developmental defects. As a result of pituitary gland secretory hormone tumors, severe life-threatening hormonal disorders that impair body functions may develop (Alkan et al., 2022).

The general and effective treatment of these problems in the pituitary gland is surgery. There are two methods to reach this area, which is difficult and risky due to its anatomical location. The first is the transcranial method, in which the pituitary gland is reached by opening the skull and traveling a long distance through the brain tissue, main cerebral vessels, and optic nerves. The second method is the transsphenoidal method, which enters through the nasal cavity, opens the sphenoid cavity, and reaches the pituitary gland. It is very preferred because of the opening of the brain with the transcranial method, the inability to control the pituitary gland fully, and the inability to perform an effective surgery. The transsphenoidal method is preferred to reach the pituitary gland more quickly than the transcranial method due to better control of the pituitary gland and less damage to the tissue during surgery (Tsuneoka et al., 2023; Trimpou et al., 2022). Complication risks are high in this method due to its anatomical location and neighborhood. Complications and rates that may be encountered after transsphenoidal surgery, taken from https://www.turknorosirurji.org.tr (2020), are given in Table 1. To perform an effective surgery in this area, which has many anatomical variations between people, it is necessary to determine the structure and shape of the Tumor in order to completely evacuate the Tumor, to determine the transsphenoidal anatomical path well for a successful surgery with minor damage to the tissues, and to determine its relationship with essential structures in the neighboring areas to reduce the risk of complications. While the operations are performed in a 3D environment during the surgery, preoperative planning is done through 2D imaging. It cannot reveal an adequate anatomy, thus reducing the success rate in surgical planning and during surgery. As a result of better revealing both the surgical area and the surgical path and neighborhoods with 3D imaging, the operation's success will increase, there will be less tissue damage, and the risk of reoperation and complications will be reduced by ensuring that the Tumor is evacuated more effectively.

Pituitary tumor surgeries are very risky surgeries. The more information about tumor size, location, proximity to optic nerves and thalamus, and closeness to the carotid artery to perform this surgery, the more successful it will be and the lower the incidence of postoperative complications. In the current Magnetic Resonance (MR) imaging methods, 3D tumor imaging cannot be performed, and blind spots may remain in the endoscope devices used during the surgery. It will be beneficial to have information about the 3D image of the Tumor, carotid artery, and optic nerves before the surgery.

Deep learning methods are more successful in processing medical images than classical methods. In 2D segmentation, the specialist doctor must select the appropriate slices from the MR image slices. In addition, the image obtained due to image processing will be two-dimensional. 3D U-Net is a new way of deep learning. This method can do the training by using much fewer images with many images that other deep learning methods need (Altun and Alkan; 2022c). Considering the difficulties of providing medical images, the method is a significant gain for the medical field. Since the method reduces the classification and then segmentation down to the pixel, it can achieve higher success, as seen from the literature studies (Egger et al., 2016). The most important unique aspect of the project is that it will segment the pituitary Tumor with a method that has not been studied before, such as 3D U-Net.

Table 1. Post-transsphenoidal complications

Complication	Ratio
Anesthesia complications	%2.8
Carotid artery rupture	%1.1
Damage to brain tissue	%1.3
Hematoma in tumor tissue that cannot be removed entirely	%2.9
Vision loss	%1.8
Paralysis in eye movements	%1.4
Cerebrospinal fluid leak	%3.9
Meningitis	%1.5
Perforation of the septum in the nose	%6.7
Nose bleeding	%3.4
Sinusitis	%8.5
Anterior pituitary hormone deficiency	%19.4
Incipient diabetes	%17.8
Death	%0.9

In this study, 3-dimensional automatic segmentation was performed using contrast-enhanced T1 sequence MR images from women diagnosed with Pituitary Tumors. Our study was limited to female patients, and the study focused on women with this disease, which disrupts the hormonal balance.

REVIEW

Various deep learning approaches have been proposed for the segmentation of brain tumor MRIs, each aiming to accurately delineate the boundaries and achieve precise segmentation. The Edge U-Net model incorporates boundary-related MRI data with the main brain MRI data to localize tumors more accurately. To enhance the performance of the segmentation model, a novel loss function that incorporates boundary information was introduced. This loss function improves the precision of the learning process and produces more accurate results. The results demonstrated that the proposed framework achieved satisfactory Dice score values compared to state-of-the-art models, effectively differentiating brain tissues with high accuracy. The Edge U-Net model achieved Dice scores of 88. 8% for meningioma, 91. 76% for glioma, and 87.28% for pituitary tumors. Based on these results, the Edge U-Net model shows promise as a diagnostic tool that can assist radiologists in accurately segmenting brain tumor tissue images (Allah et al., 2023).

These researchers delve into a thorough examination of two prominent object recognition frameworks, namely YOLOv5 and YOLOv7, utilizing cutting-edge deep learning architectures to categorize and identify brain tumors within MRI scans. This preprocessed dataset is employed to assess the performance of the deep learning models in detecting and classifying brain tumors. The results from YOLOv5 indicate a recall score of 0. 905 for box detection and 0.906 for mask segmentation, with precision scores of 0. 94 and 0. 936, respectively. Both box detection and mask segmentation achieve a mean Average Precision (mAP) of 0.947 at an Intersection over Union (IoU) threshold of 0. 5, while at an IoU threshold ranging from 0. 5 to 0. 95, they attain mAPs of 0.666 and 0. 657, respectively. On the other hand, YOLOv7 demonstrates robust performance with a box detection accuracy of 0. 936 and mask segmentation accuracy of 0.935. Across the broader IoU range of 0. 5 to 0. 95, the mAPs are 0.677 for box detection and 0. 659 for mask segmentation (Almufareh et al., 2024).

Ali Mohammad Alqudah et al. studied segmenting meningioma, glioma, and pituitary tumors using deep learning. They obtained the data set they used in their studies from "https://figshare.com/articles/brain_tumor_dataset/1512427/5". A total of 3064 T1-weighted MR images are included in this database. The number of images differs for the three different tumor types. They used 70% of the data set for training and 30% for testing. The study was studied differently with the CNN deep learning method for three different sections using original images, images obtained by cropping the tumor region, and images obtained by tumor segmentation. They created the CNN architecture themselves, and it consists of 19 layers. As a result of the procedure, the average classification success was calculated as 98% (Alqudah et al., 2019).

Jan Egger et al. state that since the pituitary gland is the manager for the secretion of hormones, an indispensable part of the body, an abnormality here affects the body negatively. They cite Cushing's disease, which is caused by a pituitary tumor, as an example. In addition, the article mentions that tumors larger than 1 mm may require surgical intervention, while tumors smaller than 1 mm can be treated with various treatment methods without surgical intervention. Their study used T1 and T2 weighted MR images of 10 patients. The tumor volume obtained by manual segmentation in the open-access 3D Slicer program and the segmentation success of the GrowCut interface of this program were compared by looking at the DICE score. They calculated a DICE score between 75% and 85% (Egger et al., 2013).

Song et al. mention that since there is no 3-dimensional imaging in the endoscope devices used in pituitary tumor surgeries performed with the transsphenoidal method, vital organs such as optic nerves and carotid arteries can be damaged during this surgery. The study aims to design a new endoscope device that displays the pituitary Tumor, optic nerves, and carotid artery using computed tomography (CT) images and gives an audible alarm when the surgeon approaches these organs during the operation. Computed tomography images were segmented using the 2D U-net deep learning method. In the preprocessing part of the study, the Tumor, optic nerves, and carotid artery were manually segmented by the specialist using the 3D Slicer program in all 1218 slices of CT images of 6 patients used for training. By preprocessing 11 augmentations from each slice, the number of extracted images was 13398. The U-net operation is divided into two parts. In the first part, 1218 images and labels were trained. In the second part, after 20% of the images obtained by augmentation were reserved for the test, the training was continued using the weights obtained in the first part. It is stated that the training process takes too much time, and the aim is to reduce it, which is the reason for the two-stage system. In the Jaccard test they used to determine the segmentation success, they achieved a success rate of up to 0.76 for the optic nerve, 0.72 for the carotid artery, and 0.75 for the Tumor (Song et al., 2019).

Victor E. Staartjes et al. emphasize that the transsphenoidal method is frequently used in pituitary tumor surgery, and the method aims to remove the Tumor altogether. However, it is emphasized that sometimes, the pituitary Tumor cannot be removed entirely due to its deepness or different complications. It is stated that machine learning methods have been studied frequently in recent years and have promising results in the medical field. Therefore, they propose a model that calculates whether the Tumor can be removed entirely after surgery using MR images of 140 transsphenoidal surgery patients. They used a deep learning network and the Knosp classification method for the proposed model. They used the Knosp method to grade the Tumor between 0 and 3. They achieved 91% success in deep learning and 81% in Knosp classification (Staartjes et al., 2018).

Yu Qian et al. used their study's 796 MR images of 149 patients. Since the CNN deep learning method used in the study would give better results with many images, they increased the number of images to 8756 by performing data augmentation. Of the 149 patients, 84 were patients with pituitary tumors, and 65 were in the control group. They randomly separated the dataset for training and testing at a ratio of 8:2. The study emphasizes that the pituitary Tumor is a relatively small organ, and its size may vary from person to person. For these reasons, it is emphasized that it is tough to detect a pituitary tumor manually, and it depends on the experience and personal interpretation of the doctor. In the preprocessing, the pituitary gland's region in the patients' images was manually segmented in 180x140 size. After the MR images were preprocessed separately for each of the Coronal, Horizontal, Sagittal, T2-weighted images, Coronal and Horizontal angles of the T1 images, they were processed in the CNN architecture they created, and the success of comprehensive segmentation was examined. In this study, in which they labeled patients with pituitary tumors and patients in the control group, they achieved an average classification success of 91% in the classification of patients with and without tumors (Qian et al., 2020).

MATERIAL

Our study is retrospective, and the dataset will be created using preoperative contrast-enhanced T1-weighted MR images of female patients who underwent pituitary tumor surgery with the transsphenoidal method in Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Neurosurgery. Necessary ethics committee permissions were obtained to create the data set. Figure 1 shows an exemplary MR image of a pituitary tumor. In the data set, MR images of 45 women diagnosed with pituitary tumors were used. There are 33 MR images, 11 in each sequence, and 1485 MR images were used for 45 patients. The size of these images is 414x393 pixels.

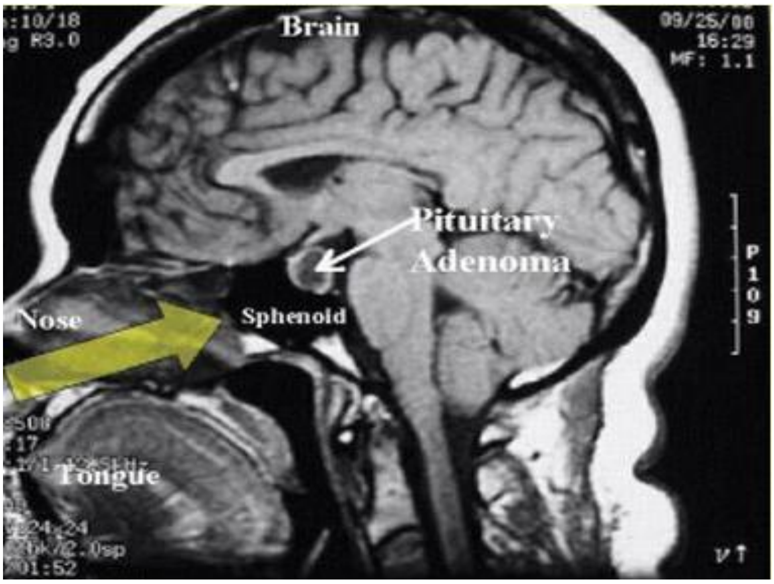

Figure 1. MR image of pituitary Tumor

METHOD

Preprocessing

The MR images in the dataset are in Digital Imaging and Communications in Medicine (DICOM) image format. The images were converted to the Neuroimaging Informatics Technology Initiative (NIFTI) format, and patient information on the image was removed. In addition, the 15-year-old specialist doctor removed the completely black part of the MR image and selected only the relevant area (ROI) (Du et al., 2023). The specialist has determined that a size 414x393 is suitable for image processing. An example image is shown in Figure 2.

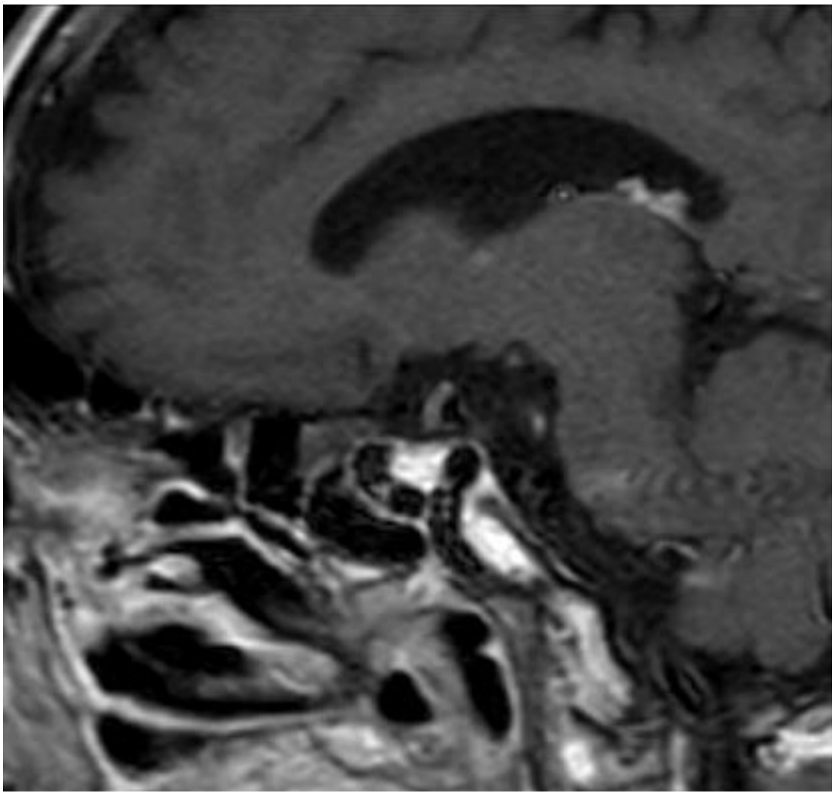

Figure 2. An exemplary MR image.

Figure 3 shows an example of manual labeling made on a 2D slice of a randomly selected patient.

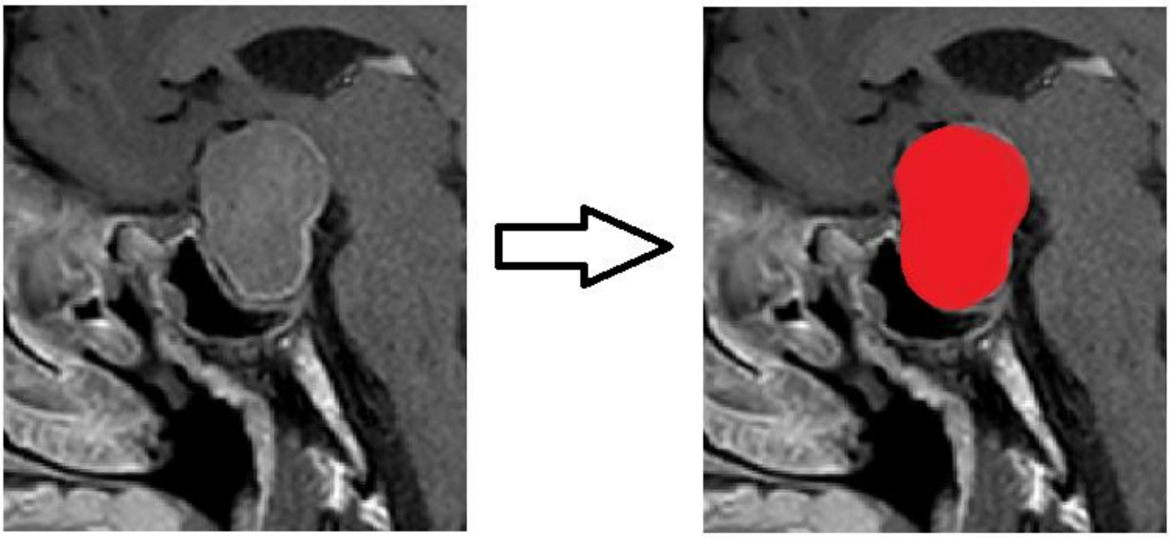

Figure 3. Manual labeling on a 2D MR image using the 3D Slicer program.

There may be noise in the MR images due to the high magnetic field used in MR imaging and the patient's movement during the shooting. One of the standard methods for removing these noises in biomedical images is the Gaussian filter (Afshari et al., 2017; Srinivasa et al., 2021).

It can be said that the Gaussian smoothing operator is a 2-dimensional convolution operator used to blur images and remove noise (Wang et al., 2022). Equation 1 contains the general formula of the Gaussian filter. Here, "σ" denotes standard deviation, "x" and "y" denotes the values on the axes.

$$G(x,y) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{x^2+y^2}{2\sigma^2}} \quad (1)$$

In this study, the necessary literature research for noise reduction (Afshari et al., 2017; Srinivasa et al., 2021; Wang et al., 2022) was made, and the Gaussian filter was applied to MR images. In Figure 4, the results were obtained by applying a Gaussian filter to the image of a patient in the data set for the "σ" value of 0.5 and 2. The "σ" value was preprocessed with the appropriate value of 2 by examining the literature (Afshariet al., 2017; Srinivasa et al., 2021; Wang et.al. (2022).

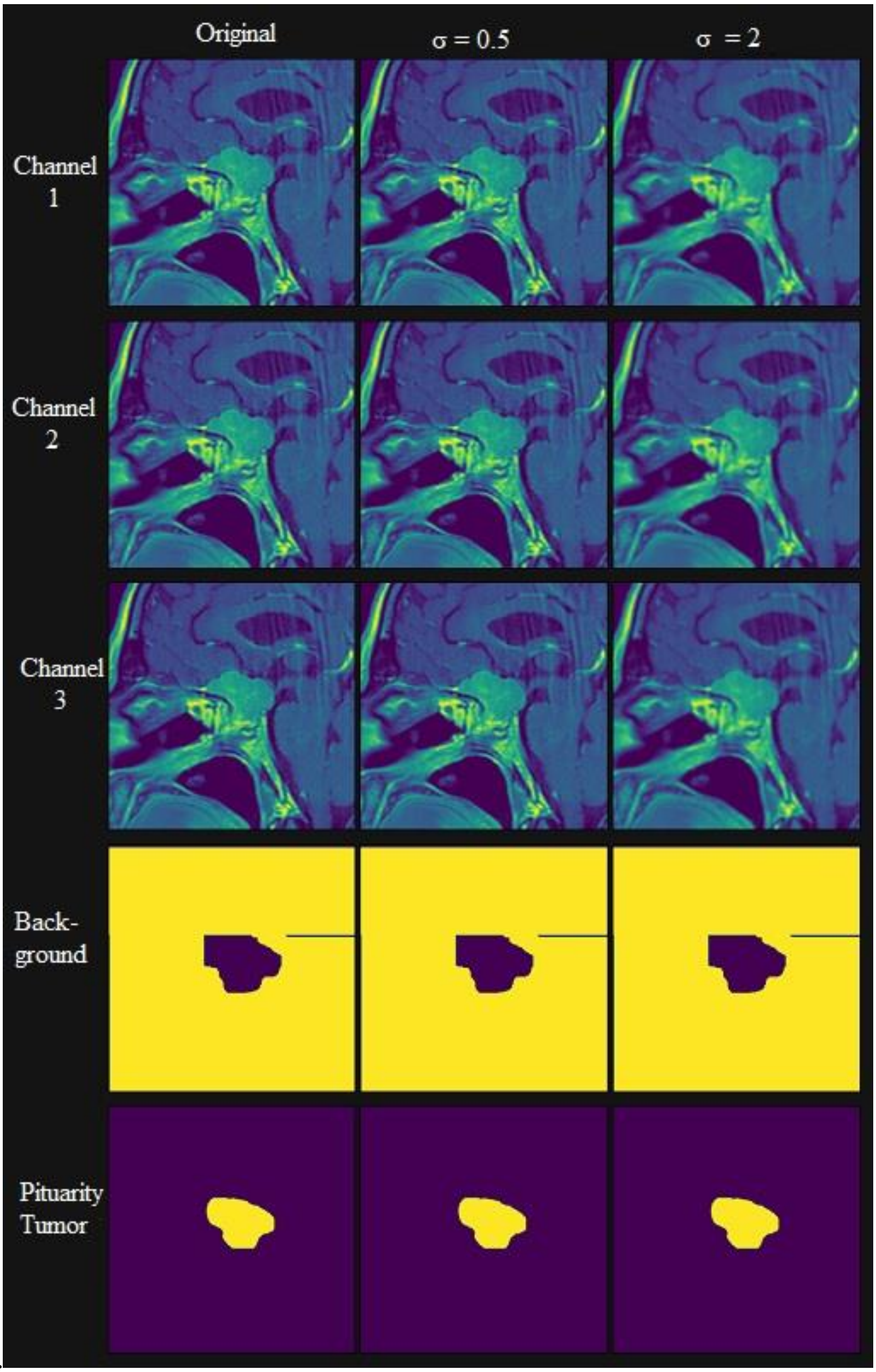

Figure 4. Images with Gaussian filter applied.

3D Slicer Program

The 3D Slicer program is a free download (https://www.slicer.org/) program that offers the opportunity to process medical images in every slice. The pituitary Tumor will be manually segmented in all slices in this project using program tools. It is straightforward to operate the program with a simple interface. It is possible to access training documents with a simple explanation on the https://www.slicer.org site. Figure 5 shows the interface image of the program (Egger, 2012).

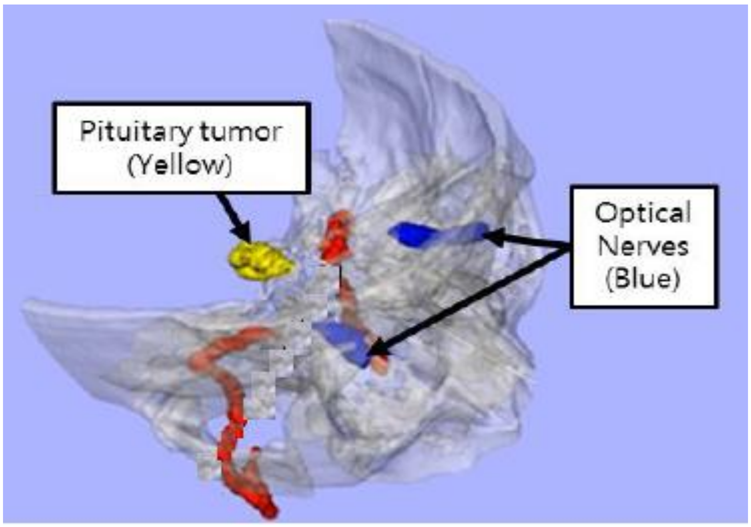

Figure 5. An example image of 3D manual segmentation with the 3D Slicer program.

3D-Unet

U-Net architecture, Convolutional Neural Network (CNN), is a deep learning method with the same logic. U-Net deep learning architecture can achieve higher success in medical images because it performs pixel-based segmentation. While CNN needs many images for training, this is less important for U-Net architecture. For example; (Song et al., 2019) used six different medical images and three different medical images to look at the segmentation success in the U-Net architecture (Çiçek et al., 2018; Song et al., 2019).

Due to the location of the pituitary gland and the tumor tissue that may occur here, and since the transsphenoidal method, one of the pituitary tumor surgery methods, is likely to damage the surrounding tissues, 3D imaging will be helpful in tumor detection and surgery. In this study, the MR images of 45 patients who underwent pituitary tumor surgery with the transsphenoidal method will be calculated using the 3D U-Net deep learning method to calculate the success of automatic tumor segmentation. In that case, each convolutional layer uses the "ReLu" activation function, while the "Fully Connected Layer" in the CNN deep learning method is not included. The first part of the architecture works by increasing the size, and the second part works by decreasing the size (Çiçek et al., 2018; Song et al., 2019).

Application Details

MR images were taken with the General Electric brand, Optima MR 360 advanced model, and 1.5 Tesla MR device.

Work was done in Python using Keras. A desktop computer with a 3.6GHz Intel(R) i7 CPU, GTX 1060TI graphics card, and 16GB GPU memory was used to train and validate the network.

Table 2 shows the hyperparameters used for training.

Table 2. Hyperparameters.

Hyperparameter Name:	Value:
Epoch	1000
Learning Rate	0,01
Batch Size	2
Optimizer	Adam
Loss Function	categorical_crossentropy
Training/Test	90/10

RESULTS

The study used 80% of the data set for training 10% for testing, and %10 for validation. Since our data set is relatively small, cross validation was not used. Since our study will continue in the future, the data set will be increased and cross validation will be performed. Of the 45 images, 40 were used for training and 5 for testing. Five pieces of data used for training were excluded from the training. Figure 6 shows the achievements of 3D automatic segmentation. The estimated pixel values stabilized after the 800th epoch. The calculated accuracy value achieved high success in the previous epochs. The Loss function, which optimizes the model's pixel classification with high success, is the 950th epoch for the validation data set (5 pieces of data), and the minimum value has been achieved.

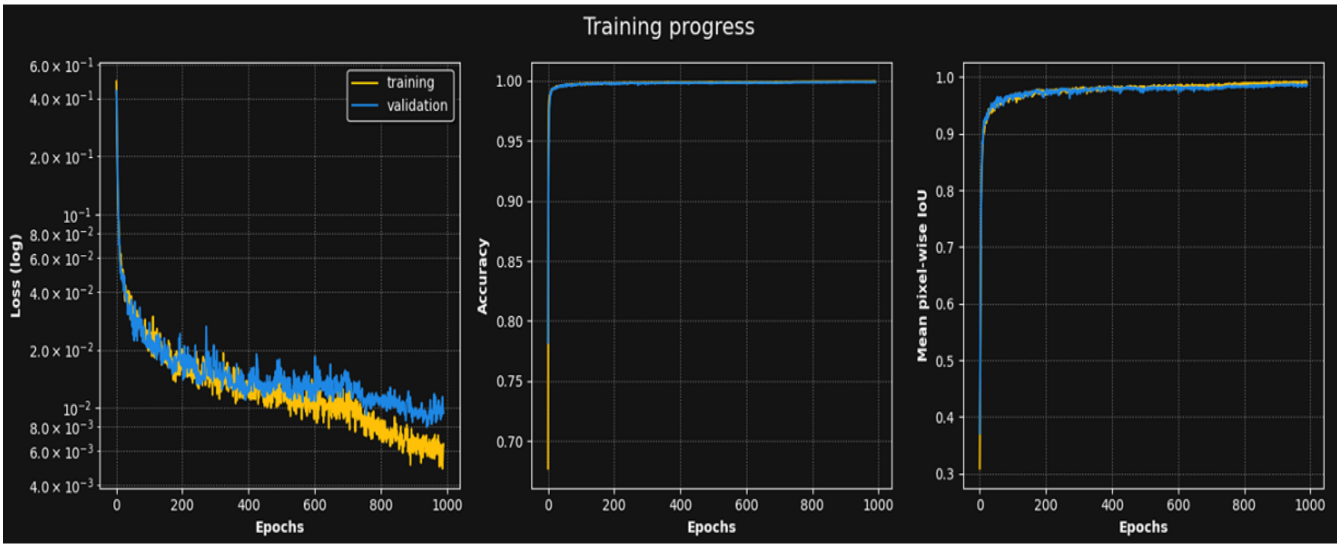

Figure 6. 3D Unet architecture.

Table 3 shows the accuracy results of 3D automatic segmentation. The IoU score of the automatic segmentation performed for five pieces of data not subject to training was relatively high, at 0.97. Although the number of pixels in the tumor area is less than in the background, a high IoU score was obtained here.

Table 3. Scores

	Background	Tumor	Mean
Train IoU score	0.99	0.97	**0.98**
Validation IoU score	0.97	0.96	**0.97**

In our study, the pituitary tumor image of patient 3, obtained as a result of manual and automatic segmentation, is shown in Figure 7. Since there are 11 slices in each of the sagittal, axial, and frontal images in each data, 11 slices will be shown separately in Figure 7. The areas shaded in orange in each slice show the pixels that manual and automatic segmentation collectively identify. It is possible to interpret from the excess of orange scans that the pixels are correctly classified in each slice. The areas scanned in red on the slices show the pituitary Tumor manually labeled by the specialist doctor. Green areas show pixels that are not manually labeled and are classified as pituitary tumors by 3D-Unet. When 11 slices are examined in detail, the number of misclassified pixels is relatively low. A few pixels that cannot be manually labeled and accurately predicted by the model are visible in the 10th slice. A small number of pixels, not in manual labeling and classified as pituitary tumors by the model, are slightly visible in each of the 11 slice images.

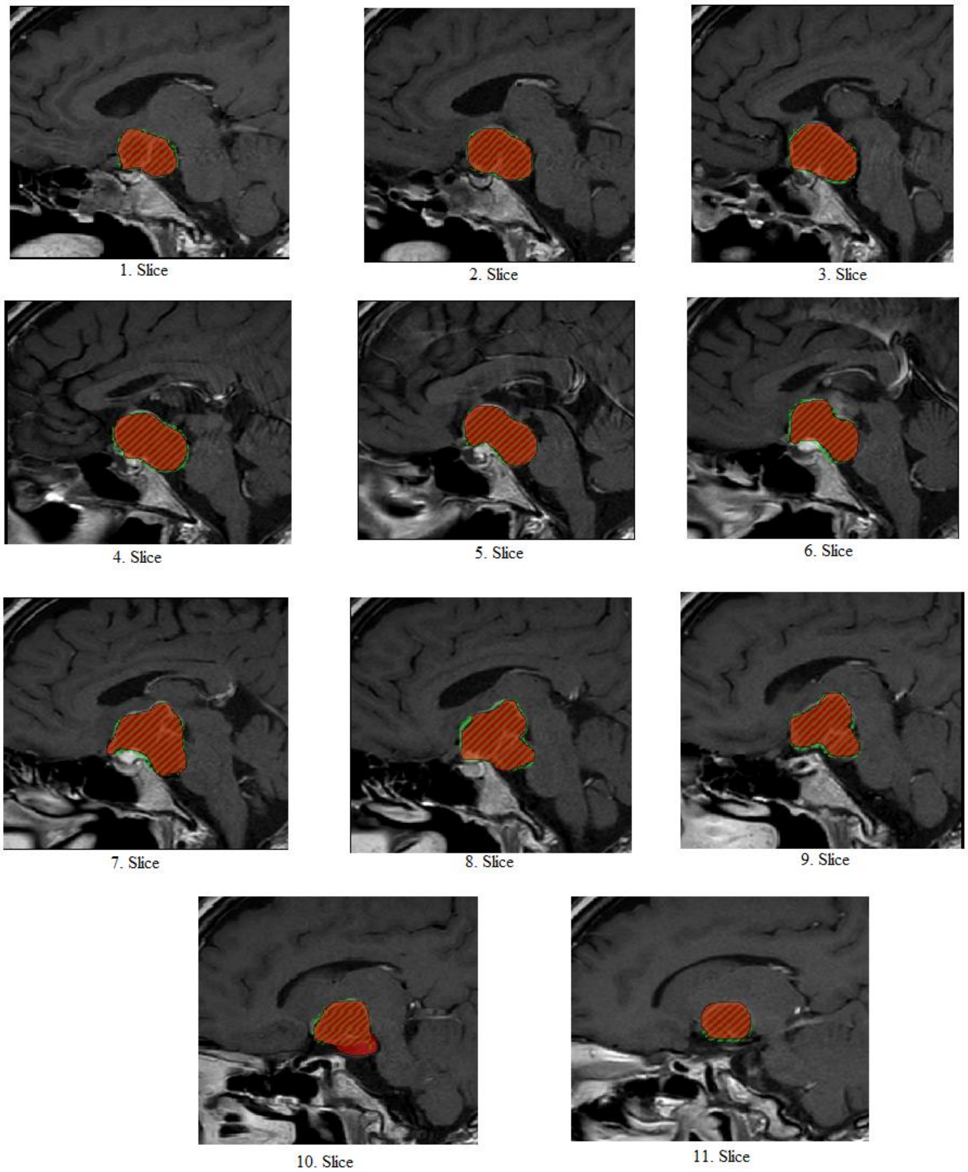

Figure 7. The result of patient No. 3 was obtained by manual and automatic segmentation.

CONCLUSION

Hormonal balance is essential for people to lead a healthy life. Disruption of the hormonal balance can affect the relevant organs and indirectly affect all organs. The pituitary gland regulates the release of hormones, one of the most essential parts of a healthy life. One of the effects that disrupt the activities of the pituitary gland is tumor formation. Diseases such as Cushing's, acromegaly, and growth hormone deficiency may occur as a result of a pituitary tumor. In addition, the Tumor may act as a pituitary in some cases causing the release of hormones to a level that harms human health. Hormonal balance is more important in women due to conditions such as fertility. Therefore, more attention is paid to hormone balance in women, and the hormone values related to the diagnosis of any disease are becoming more critical. The Pituitary Gland, which is the manager of hormone release, becomes even more demanding for women.

The pituitary gland is located at the base of the brain, behind the bridge of the nose, in the bony cavity called the Sella Turcica (Turkish saddle). As can be seen in Figure 5, the brain has the deepest place. Again, as shown in Figure 5, it is very close to the optic nerves. The pressure of the Tumor to be formed on the optic nerves may also affect the person's visual function. The operation to clean the Tumor is quite tricky due to the gland's location. Transsphenoidal is a method that cleans the Tumor by reaching the pituitary through the nose. Since this method is complex and requires good expertise, it can be performed in a limited number of centers. It is a complicated operation due to the location of the Tumor. The proximity of the pituitary to the optic nerves makes it mandatory not to damage the nerves while the Tumor is being cleaned. In addition, removing the Tumor located in the deepest part of the brain will be tough.

Expert decision support systems are objective systems that aim to help the doctor with diagnosis and treatment by using computer software. Considerable progress has been made in processing biomedical images, especially with the deep learning methods becoming competent. Namely, 3D automatic classification and segmentation can be done on images. It is understood from here that detailed information about the location and shape of the Tumor can be obtained using 3D automatic segmentation. This information would not be available if only 2D segmentation were done on a single slice. Classifying pituitary tumors using the 3D-Unet network in the women we recommend is precious in this respect. In this way, the surgical operation can be planned in detail. In this study, research was carried out with computer software that can automatically 3D segment the pituitary tumors of female patients in whom hormonal activities are more important. The high semantic segmentation success of up to 98% objectively demonstrates the success of the proposed model.

Funding Statement

Funding still needs to be received for the study.

Ethics Committee Certificate

Our study is retrospective, and data were obtained from patients who applied to Kahramanmaras Sutcu Imam University Faculty of Medicine, Department of Neurosurgery. Ethics Committee approval was obtained from the Brain and Nerve Surgery institution to obtain the data (Session Number 2021/04, Protocol Number 07).

Thanks

REFERENCE

Afshari, M., Yang, A., Bega, D. (2017). Motivators and Barriers to Exercise in Parkinson's Disease. *Journal of Parkinson's Disease,* 7(4), 703–711. https://doi.org/10.3233/jpd-171173

Alkan, F., Ersoy, B., Kızılay, D. Ö., Ozyurt, B. C., Coskun, S. (2022). Evaluation of cardiac structure, exercise capacity, and electrocardiography parameters in children with partial and complete growth hormone deficiency and their changes with short-term growth hormone replacement therapy. *Pituitary*, 26(1), 115–123. https://doi.org/10.1007/s11102-022-01295-z

Alqudah, A. M., Alquraan, H., Abu-Qasmieh, I., Alqudah, A., Al-Sharu, W. (2019). Brain Tumor Classification Using Deep Learning Technique - A Comparison between Cropped, Uncropped, and Segmented Lesion Images with Different Sizes. *International Journal of Advanced Trends in Computer Science and Engineering*, 8(6), 3684–3691. https://doi.org/10.30534/ijatcse/2019/155862019

Altun, S., Alkan, A. (2022c). LSS-net: 3-dimensional segmentation of the spinal canal to diagnose lumbar spinal stenosis. *International Journal of Imaging Systems and Technology*, 33(1), 378–388. https://doi.org/10.1002/ima.22807

Ciavarra, B., McIntyre, T., Kole, M. J., Li, W., Yao, W., Guttenberg, K. B., Blackburn, S. L. (2023). Antiplatelet and anticoagulation therapy and the risk of pituitary apoplexy in pituitary adenoma patients. *Pituitary*. https://doi.org/10.1007/s11102-023-01316-5

Çiçek, Ö., Abdulkadir, A., Lienkamp, S. S., Brox, T., Ronneberger, O. (2016). 3D U-Net: Learning Dense Volumetric Segmentation from Sparse Annotation. *In Lecture Notes in Computer Science* (pp. 424–432). Springer Science+Business Media. https://doi.org/10.1007/978-3-319-46723-8_49

Egger, J., Zukić, D., Freisleben, B., Kolb, A., Nimsky, C. (2013). Segmentation of pituitary adenoma: A graph-based method vs. a balloon inflation method. *Computer Methods and Programs in Biomedicine*, 110(3), 268–278. https://doi.org/10.1016/j.cmpb.2012.11.010

Geer, E. B. (2023). Medical therapy for refractory pituitary adenomas. *Pituitary*. https://doi.org/10.1007/s11102-023-01320-9

Qian, Y., Qiu, Y., Li, C., Wang, Z., Cao, B., Huang, H., Ni, Y., Chen, L., Sun, J. (2020). A novel diagnostic method for pituitary adenoma based on magnetic resonance imaging using a convolutional neural network. *Pituitary*. https://doi.org/10.1007/s11102-020-01032-4

Sharma, M., Wang, D., Scott, V., Ugiliweneza, B., Potts, K., Savage, J., Boakye, M., Andaluz, N., Williams, B. J. (2023). Intraoperative MRI use in transsphenoidal surgery for pituitary tumors: Trends and healthcare utilization. *Journal of Clinical Neuroscience*, pp. 111, 86–90. https://doi.org/10.1016/j.jocn.2023.03.009

Simander, G., Dahlqvist, P., Oja, L., Eriksson, P. O., Lindvall, P., Koskinen, L. D. (2023). Intrasellar pressure is related to endocrine disturbances in patients with pituitary tumors. *World Neurosurgery*. https://doi.org/10.1016/j.wneu.2023.03.085

Song, H., Yoon, H., Lee, S., Hong, C., Yi, B. (2019). Surgical Navigation System for Transsphenoidal Pituitary Surgery Applying U-Net-Based Automatic Segmentation and Bendable Devices. *Applied Sciences*, 9(24), 5540. https://doi.org/10.3390/app9245540

Srinivasa Reddy. K, Jaya. T. (2021). Medical Image Retrieval using Two-Dimensional PCA. International *Journal of Innovative Technology and Exploring Engineering (IJITEE)*, 9(4), 1852-1856. https://doi.org/10.35940/ijrte.D1152.018520

Staartjes, V. E., Serra, C., Muscas, G., Maldaner, N., Akeret, K., Van Niftrik, C. H. B., Fierstra, J., Holzmann, D., Regli, L. (2018). Utility of deep neural networks in predicting gross-total resection after transsphenoidal surgery for pituitary adenoma: a pilot study. *Neurosurgical Focus*, 45(5), E12. https://doi.org/10.3171/2018.8.focus18243

Trimpou, P., Backlund, E., Ragnarsson, O., Skoglund, T., T, H., Gudnadottir, G., Carlqvist, J., Farahmand, D. (2022). Long-Term Outcomes and Complications from Endoscopic Versus Microscopic Transsphenoidal Surgery for Cushing's Disease: A 15-Year Single-Center Study. *World Neurosurgery*, 166, e427–e434. https://doi.org/10.1016/j.wneu.2022.07.027

Tsuneoka, H., Tosaka, M., Yamaguchi, R., Tanaka, Y., Mukada, N., Shimauchi-Ohtaki, H., Aihara, M., Shimizu,

T., Yoshimoto, Y. (2023). The Significance of the Intercarotid Distances for Transsphenoidal Pituitary Surgery: A Magnetic Resonance Imaging Study. *World Neurosurgery*. https://doi.org/10.1016/j.wneu.2023.04.009

Du, Y., Zhang, S., Fang, Y., Qiu, Q., Zhao, L., Wei, W., Tang, Y., & Li, X. (2022). Radiomic Features of the Hippocampus for Diagnosing Early-Onset and Late-Onset Alzheimer's Disease. *Frontiers in Aging Neuroscience*, (), n/a.

Almufareh, F.M., Imran, M., Khan, A., Humayun, M., Asim, M. (2024). Automated Brain Tumor Segmentation and Classification in MRI Using YOLO-Based Deep Learning. *IEEE Access*. 12, 16189 – 16207. DOI: 10.1109/ACCESS.2024.3359418