Apparent Diffusion Coefficients in Evaluation of Pediatric Brain Tumors

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Background: *MRI, which has high sensitivity in brain tumor detection, cannot reliably determine tumor grading or histology. Diffusion-weighted imaging and apparent diffusion coefficients (ADCs) provide information of tumor cellularity that can correlate with grading.*
Objective: *To investigate ADCs in differentiation low-grade from high-grade pediatric brain tumors.*
Material and Method: *Preoperative MRI, DWI, and ADC images of pediatric patients with pathologically proven brain tumors were retrospectively reviewed at a university hospital in two-year periods and classified into low-grade and high-grade categories. Regions of interest were placed manually at the center and periphery of the solid tumor regions, then ADC values were calculated at "b" values = 0, 1000 sec/mm^2.*
Results: *The ADC values were calculated in 15 patients, which included 12 males and three females with an age range from three to 14 years. Seven and eight were with low- and high-grade tumors respectively. The ADC values of low-grade tumors were markedly higher than those of high-grade tumors with statistically significant differences by all methods of measurements at the central, peripheral, and average areas on Man-Whitney U test, with p-values of 0.037, 0.009, and 0.021, respectively.*
Conclusion: *MRI with ADCs for preoperative pediatric tumor evaluation may be useful for predicting tendency of tumor grading and surgical planning.*

Keywords: *Apparent diffusion coefficients, Pediatric, Brain tumor*

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Brain tumors are the solid neoplasm in childhood. They are third to the leukemia and lymphoma in overall frequency among childhood cancers, accounting for 7.6 per million[1]. This encompass a heterogeneous histopathology. Conventional, magnetic resonance imaging (MRI) is a non-invasive anatomical assessment tool for characterization, localization, and evaluation of tumor extension. In general, malignant tumors are usually enhanced after intravenous contrast injection and show peritumoral edema whereas benign tumors usually show faint or no enhancement and peritumoral edema. However, differentiation between these two types of tumor may occasionally be difficult. The tumors that appear similar radiographically may have a very different histology or biologic behavior[2].

Advanced MR imaging techniques-perfusion imaging, diffusion-weighted imaging (DWI) and MR spectroscopy (MRS) allow assessment of tissue characteristics, such as vascular endothelial proliferation, cellular, and chemical compounds of the mass respectively, which are the important parameters in the grading of the brain tumor[3]. Proton MRS has been used to characterize tumor grade, has been correlated with histology, and assists in distinguishing tumor progression from treatment-related changes[4].

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However, there is a considerable overlap among different tumor types and tumor grades in characterizing pediatric brain tumors[5]. In addition, they are time-consuming for scanning and processing of data and intratumoral heterogeneity complicates the results. Perfusion imaging allows noninvasive assessment of tumor neoangiogenesis and hypervascularity by measuring regional cerebral blood volume, cerebral blood flow, and permeability[3,6]. In general, low-grade gliomas have significantly lower cerebral blood volume compared to higher-grade gliomas[7]. However, pediatric patients have yielded inconsistent results[8].

DWI is a technique that allows evaluation of microscopic water diffusion within tissue. The apparent diffusion coefficients (ADCs) is a measure of the ability of tissue to restrict water diffusion. DWI and ADC maps have proven useful in evaluation of cerebral infarction and distinguishing brain abscess from brain tumor and arachnoid cyst from epidermoid tumor[9,10]. Previous studies showed that ADC values had been used to grade glioma and to differentiate some brain tumors in adult and pediatric patients, though some reported studies demonstrated conflicting results[12-15].

The purpose of the present study was to investigate ADC values in term of differentiation low-grade from high-grade pediatric brain tumors.

Material and Method

The present study was approved by Ramathibodi Hospital's Institutional Review Board. The authors retrospectively reviewed all pediatric patients (age less than 15 years) with newly diagnosed brain tumors at a university hospital during consecutive two-year periods. Preoperative conventional MRI and diffusion-weighted images of the brain were initially performed in our institution. Each patient included in the present study had mass containing solid portion. The resections were performed at our institution to confirm histopathologic analysis. Patients who had preoperative examination at other institutions, who were treated before imaging, or who had entirely cystic tumors were excluded.

The specimens were retrospectively confirmed by a board-certified neuropathologist. Furthermore, they described the histolopathologic subtypes. He was blinded to the MR findings and diffusion-weighted images. The tumors were graded using World Health Organization (WHO) criteria. All tumors were classified as benign or low-grade (WHO grade I-II) and malignant or high-grade (WHO grade III-IV) categories.

All patients were examined using a 1.5-Tesla MR scanner (Signa HDxt; General Electric Healthcare, Milwaukee, WI, USA) or 3.0-Tesla MR scanner (Achieva; Philips Medical System, Best, The Netherlands). Conventional MRI with gadolinium of the brain was performed in each patient with protocol that included sagittal non-contrast T1-weighted, axial fast spin-echo T2-weighted, axial fluid-attenuated inversion recovery (FLAIR), and post-contrast enhanced axial, coronal, and sagittal T1-weighted images. Before the contrast administration was done, diffusion-weighted images had been obtained by using an axial echo-planar SE sequence. The DWI protocol was performed on a 1.5-T system with following parameters: 6,000/90 (TR/TE); "b" value of 0, 1000 s/mm^2: field of view, 24x24 cm; matrix 128x128; slice thickness, 5 mm; section gap, 1.5 mm. The DWI protocol was performed on a 3-T system, consisted of the following parameters: 4,600/86 (TR/TE); "b" value of 0, 1000 s/mm^2: field of view, 24x24 cm; matrix 136x136; slice thickness,

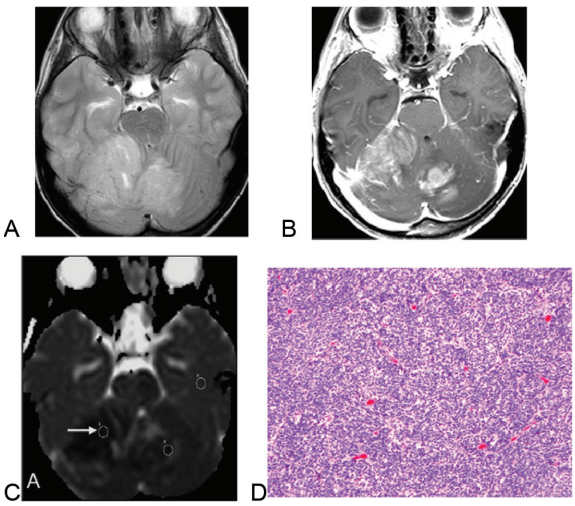

Fig. 1 A 8-year-old boy with medulloblastoma.
A) Axial T2-weighted image reveals a hyperintense right cerebellar and vermian mass.
B) Axial contrast-enhanced T1-weighted image shows heterogeneous enhancement of the tumor.
C) Apparent diffusion coefficient (ADC) map reveals hypointensity at the mass, representing restricted diffusion of water, ROI was placed (arrow).
D) The photomicrograph of the specimen shows densely packed cells with round-to-oval shaped hyperchromatic nuclei surrounded by scanty cytoplasm, which is typically called small round blue cell tumor.

5 mm; section gap, 0 mm. Post-processing of ADC maps was performed automatically on the MR scanner.

The authors used axial T2-weighted and contrast-enhanced T1-weighted images to define the slice to be analyzed and to define enhancing solid portion from the regions of cyst or necrosis, then was matched to the ADC maps. ROIs (regions of interest) were manually positioned at the central and peripheral regions of the solid portion by trying to avoid placement in the necrotic or cystic areas. The control ADC values were obtained by placing ROI in the normal-appearing white matter in the same image (Fig. 1). All ADC values were automatically calculated and expressed in 10^{-3} mm^2/s. The area of ROI was approximately 36 to 40 mm^2. The radiologist placing ROIs was blinded to the tumor histology.

Comparison of obtained normal brain and tumor ADC values between the two groups were performed with Man-Whitney U test. The differences were considered statistically significant at p-value less than 0.05.

Results

Fifteen patients were enrolled in the present study. There were 12 male (80%) and four female (20%) patients. The mean age was 8.3±3.6 years with a range of three to 14 years. The demographic data, tumor histology, location, WHO grading and ADC values are summarized in Table 1.

Seven patients had pathologically proved low-grade brain tumor and eight patients had high-grade brain tumor according to WHO classification. The locations of the tumors were infratentorial in nine patients, and supratentorial in six patients. The normal appearing brain ADC values among the patients with low-grade (range 0.72-0.89 $x10^{-3}$ mm^2/s) and high-grade (range, 0.66-1.04 $x10^{-3}$ mm^2/s) tumors were not significantly different (p = 0.202) (Table 2). The ADC values for the low-grade brain tumors obtained by using center-ROI, peripheral ROI and average ROI ranged from 1.23-1.99 $x10^{-3}$ mm^2/s, 0.90-1.96 $x10^{-3}$ mm^2/s and 1.10-1.98 $x10^{-3}$ mm^2/s, respectively. The ADC values for the high-grade brain tumors obtained by using center-ROI, peripheral ROI and average ROI ranged from 0.54-2.39 $x10^{-3}$ mm^2/s, 0.65-1.26 $x10^{-3}$ mm^2/s and 0.60-1.67 $x10^{-3}$ mm^2/s, respectively. The median ADC values among the low-grade brain tumors obtained by using center-ROI, peripheral ROI and average ROI were 1.58, 1.30, and $1.50x10^{-3}$ mm^2/s, and interquartile range were 0.64, 0.66, and $0.69x10^{-3}$ mm^2/s, respectively.

Table 1. Demographic data, tumor histology, WHO grade, location and apparent diffusion coefficient (ADC) values of tumors and normal appearing brain

Patient No. age/sex	Tumor histology	WHO grade	Location	ADC tumor core	ADC tumor periphery	ADC tumor average	ADC of normal brain
1. 10 y/F	JPA	Low	Cerebellum	1.50	1.30	1.40	0.82
2. 7 y/F	SEGA	Low	Lateral ventricle	1.94	1.75	1.85	0.72
3. 3 y/M	Meningioma	Low	Frontal lobe	1.30	0.90	1.10	0.79
4. 3 y/M	Ependymoma	Low	Fourth ventricle	1.23	1.09	1.16	0.73
5. 10 y/M	JPA	Low	Cerebellum	1.80	1.19	1.50	0.87
6. 6 y/M	Ganglioglioma	Low	Frontal lobe	1.99	1.96	1.98	0.85
7. 7 y/M	Astrocytoma	Low	Pons	1.58	1.47	1.53	0.89
8. 8 y/F	AA	High	Parietal lobe	2.39	0.95	1.67	0.77
9. 8 y/M	GBM	High	Pons	1.28	0.90	1.09	0.78
10. 12 y/M	Germinoma	High	Basal ganglion	0.69	0.75	0.72	0.66
11. 5 y/M	Medulloblastoma	High	Cerebellum	1.26	1.04	1.15	0.79
12. 14 y/M	PNET	High	Temporal lobe	1.24	1.26	1.25	1.04
13. 6 y/M	Medulloblastoma	High	Cerebellum	0.54	0.65	0.60	0.82
14. 9 y/M	Medulloblastoma	High	Cerebellum	0.81	0.80	0.81	0.71
15. 10 y/M	GBM	High	Pons	0.76	0.73	0.75	0.70

ADC values were expressed in $x10^{-3}$ mm^2/s.

JPA = juvenile pilocytic astrocytoma; AA = anaplastic astrocytoma; SEGA = subependymal giant cell astrocystoma; PNET = primitive neuroectodermal tumor; GBM = glioblastoma multiforme

The median ADC value among high-grade tumors obtained by using center-ROI, peripheral ROI and average ROI were 1.03, 0.85, and 0.95x10^{-3} mm^2/s and interquartile range were 0.57, 0.28, and 0.50 and x10^{-3} mm^2/s, respectively (Fig. 2-4). There are statistically significant differences in the median ADC values in all measurements among the two tumor groups (p = 0.037, 0.009 and 0.021, respectively) (Table 2). In addition, there is statistically significant difference in median ADC values of both brain tumor groups and normal appearing brain (p = 0.002) (Fig. 5).

Discussion

Diffusion-weighted imaging (DWI) is a technique that exploits the molecular mobility of water molecules within the tissue. Diffusion is a property related to cellularity because free water diffusivity is restricted by an increased number of cells. The greater is the cellularity impeding water mobility, the more

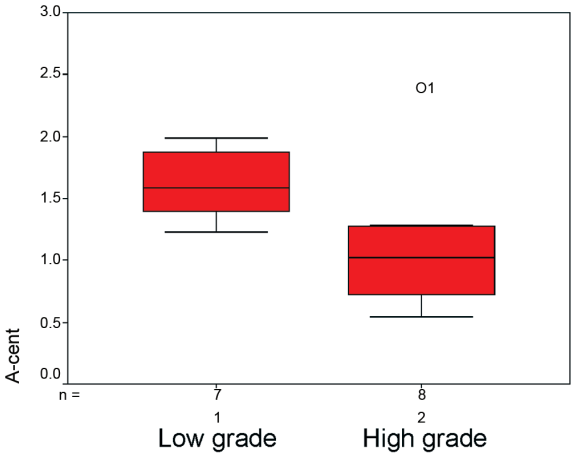

Fig. 2 Box plots comparing ADC values of patients with low-grade (n = 7) to high-grade brain tumors (n = 8). The horizontal line indicates the median, and the box indicates the interquartile range. The ADCs were measured at the center of the tumor.

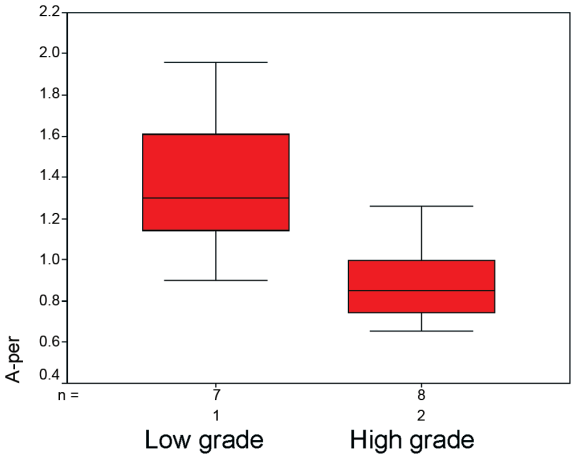

Fig. 3 Box plots comparing ADC values of patients with low-grade (n = 7) to high-grade brain tumors (n = 8). The horizontal line indicates the median and the box indicates the interquartile range. The ADCs were measured at the periphery of the tumors.

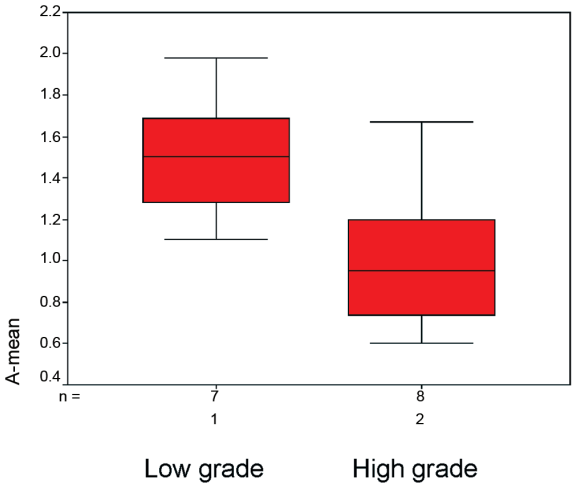

Fig. 4 Box plots comparing averaged ADC values of patients with low-grade (n = 7) to high-grade brain tumors (n = 8). The horizontal line indicates the median, and the box indicates the interquartile range.

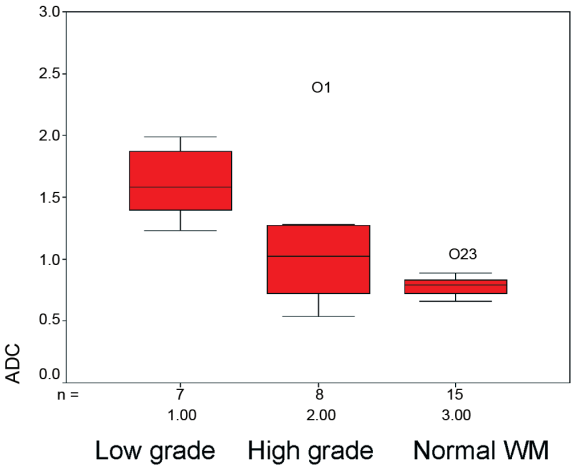

Fig. 5 Box plots comparing averaged ADC values of patients with low-grade (n = 7) to high-grade brain tumors (n = 8) and normal appearing brain (n = 15). The horizontal line indicates the median, and the box indicates the interquartile range.

Table 2. Statistically significant difference of ADC values among tumors and normal appearing brain

Parameter	Low-grade tumor		High-grade tumor		p-value
	Median	Interquartile	Median	Interquartile	
ADC tumor core	1.58	0.64	1.03	0.57	0.037
ADC tumor peripheral	1.30	0.66	0.85	0.28	0.009
ADC tumor average	1.50	0.69	0.95	0.50	0.021
ADC of normal WM	0.82	0.14	0.78	0.11	0.202

ADC values were expressed in $x10^{-3}$ mm^2/sec

restricted is the movement. Diffusion-based images can be displayed as DWI and ADC map. The ADC value is a measure of the ability of tissue to restrict water diffusion. In DWI, areas with restricted diffusion shows hyperintense, whereas ADC values become smaller.

In the present study, the authors have expanded the study to measure ADC values in different histologic subtypes, locations and grading of pediatric brain tumors and classified into low-grade and high-grade categories. The ADC values were abnormally distributed. Therefore, the median and interquartile ranges were used to substitute mean and standard deviation (SD). The averaged median ADC values of the low-grade brain tumors were markedly higher than those of high-grade brain tumors with statistically significant differences in all methods of measurements. The findings of the present study were similar to the previously published reports that have demonstrated that brain neoplasm with higher cellularity or total nuclear area shows a significant reduction in ADCs and a markedly increased signal on DWI[12]. ADC values are inversely correlated with tumor grade, i.e. low-grade tumors have higher ADCs than high-grade tumors, especially astrocytic tumor[13,14]. ADC values can be helpful for differentiation of some brain tumors in specific locations, such as glioblastomas from lymphomas, meningiomas from schwannomas, and common pediatric cerebellar brain tumors as juvenile pilocytic astrocytoma from medulloblastoma or ependymoma[15,16]. However, Kono et al[17] showed that ADC values could not be used in individual cases to differentiate tumor subtypes reliably. In the present study, the authors found that 50% of the ADC values from the tumor of each group were not overlapped. However, if we looked for the distribution differences, we could see some overlap between two tumor groups. A reason may be that the brain tumors appear heterogeneous. ROIs could not be precisely placed at the solid tumor portion and small necrotic portions of high-grade tumors which ADC values can be significantly higher leading to lower estimation of cellularity.

At present, diffusion-tensor imaging (DTI) is an adaptation of DWI, which is a more sophisticated quantitative form of diffusion imaging. In DTI, DWI data are acquired in at least six directions, not only an absolute measure of average water diffusion in each voxel (ADC) but also a measure of water diffusion along different axis (diffusion anisotropy). Therefore, DTI allows for visualization of the location, orientation, and integrity of white matter tracts in the brain. DTI gives better definition of the relationship between tumor, peritumoral changes, and white matter tracts than standard pulse sequence[18-20]. However, the resolution is limited. Furthermore, only larger pathways can be identified[21]. In addition, DTI requires additional post-processing steps.

A limitation of the present study included the small number of patients because the tumors of the central nervous system are relatively uncommon in children. Moreover, not all children were referred to a university center and some of them had preoperative examinations at other institutions.

Conclusion

Apparent diffusion coefficients between low-grade and high-grade pediatric brain tumors are statistically significantly different, although some overlapping occurs. ADC value measurements are simple, less time consuming and readily available techniques in commercial MR scanner. Tumor characteristics on conventional MR imaging with adjunctive information of ADC values might play a preoperative guideline in predicting the tendency of the tumor grading and surgical planning.

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Potential conflicts of interest

None.

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การใช้ค่าสัมประสิทธิ์การแพร่กระจายของน้ำในการประเมินเนื้องอกสมองในเด็ก

โลจนา ตันติยาทร, บดินทร์ นันทวาสน์, นงนุช ศิริชัยนันท์, นพดล ลาภเจริญทรัพย์, อนันนิตย์ วิสุทธิพันธ์, สุรเดช หงส์อิง

ภูมิหลัง: *การตรวจด้วยเครื่องสร้างภาพจากคลื่นแม่เหล็กไฟฟ้าพื้นฐาน (MRI) ให้ความไวสูงในการตรวจหาเนื้องอกในสมอง แต่ไม่สามารถบอกระดับความร้ายแรงหรือจุลกายวิภาคศาสตร์เนื้อเยื่อของเนื้องอกได้ การตรวจโดยใช้เทคนิคของการแพร่กระจายของน้ำ (Diffusion-Weighted Image-DWI) และการวัดค่าสัมประสิทธิ์การแพร่กระจายของน้ำ (Apparent Diffusion Coefficients-ADCs) จะให้ข้อมูลเกี่ยวกับความหนาแน่นของเซลล์ในเนื้องอกซึ่งอาจมีความสัมพันธ์กับระดับความร้ายแรงของเนื้องอก*

วัตถุประสงค์: *เพื่อศึกษาว่า ADCs จะช่วยวินิจฉัยแยกระหว่างเนื้องอกที่มีระดับความร้ายแรงต่ำกับสูงในกลุ่มผู้ป่วยเด็ก*

วัสดุและวิธีการ: *ได้ทำการศึกษาแบบย้อนหลังในผู้ป่วยเด็กอายุน้อยกว่า 15 ปี ที่ได้ทำการตรวจ MRI ร่วมกับ DWI และ ADCs ก่อนการผ่าตัดที่โรงพยาบาลมหาวิทยาลัยแห่งหนึ่งและผลการตรวจทางพยาธิวิทยายืนยันว่าเป็นเนื้องอกสมอง มีระยะเวลาการศึกษาติดต่อกัน 2 ปี โดยแบ่งกลุ่มเนื้องอกสมองเป็นระดับความร้ายแรงตามองค์การอนามัยโลก (World Health Organization-WHO) เป็น 2 เกรด คือ เกรดต่ำ (WHO grade I-II) และเกรดสูง (WHO grade III-IV) ทำการวาดตำแหน่งที่สนใจด้วยมือลงบนบริเวณตรงกลางและบริเวณขอบของเนื้องอกตรงที่เป็นส่วนเนื้อเยื่อแข็ง ร่วมกับวางที่บริเวณเนื้อเยื่อปกติในภาพ ADC เดียวกัน จากนั้นคำนวณหาค่า ADCs ที่ b-value = 0, 1000 วินาที/ตารางมิลลิเมตร และหาค่าเฉลี่ยของเนื้องอกทั้ง 2 ตำแหน่ง*

ผลการศึกษา: *สามารถวัด ADCs ที่ตำแหน่งดังกล่าวในผู้ป่วยที่ทำการศึกษา 15 ราย (ชาย 12 ราย หญิง 3 ราย) ช่วงอายุ 3-14 ปี โดยที่ผู้ป่วย 7 ราย มีเนื้องอกสมองในเกรดต่ำ และ 8 ราย มีเนื้องอกอยู่ในระดับเกรดสูง ค่า ADCs ของเนื้องอกเกรดต่ำมีค่าสูงกว่าค่า ADCs ในเนื้องอกเกรดสูงอย่างมาก และมีนัยสำคัญทางสถิติทั้งที่ตำแหน่งตรงกลาง ที่ขอบของเนื้องอก หรือ ค่าเฉลี่ยของทั้งสองตำแหน่ง โดยมีค่า p = 0.037, 0.009 และ 0.021 ตามลำดับ แม้ว่าจะมีค่า ADCs ซ้อนกันบ้างระหว่าง 2 กลุ่ม*

สรุป: *การวัดค่า ADCs ทำได้ค่อนข้างง่ายและเชื่อถือได้ การตรวจ MRI พื้นฐานร่วมกับการวัดค่า ADCs ตรงตำแหน่งที่สงสัยว่าเป็นก้อนเนื้องอกในเด็กก่อนผ่าตัด มีประโยชน์ในการคาดการณ์แนวโน้มระดับความร้ายแรงของเนื้องอกและสามารถช่วยศัลยแพทย์ในการวางแผนการผ่าตัด*