의학석사 학위논문

생체 우측 간이식 기증 대규모 코호트에서 딥러닝 보조 CT volumetry 를 이용한 우측 간 이식편 무게 예측의 정확도 및 효율성

Accuracy and efficiency of right liver graft weight estimation using deep learning algorithm-assisted computed tomography volumetry for living donor liver transplantation

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이 논문을 의학석사학위 논문으로 제출함

2022 년 2 월

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영문요약

Accuracy and efficiency of right-lobe graft weight estimation using deep learning algorithm-assisted computed tomography volumetry for living donor liver transplantation

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Background: CT volumetry has been widely used for graft weight estimation in living donor liver transplantation (LDLT), and deep learning algorithm (DLA) allowing for automated liver segmentation on CT may improve its efficiency. However, the accuracy of CT volumetry in graft weight estimation has not been well determined

Purpose: To evaluate the accuracy of deep learning algorithm (DLA)-assisted CT volumetric estimation of graft weight in a large cohort of living donor liver transplantation (LDLT) donors who donated right liver graft.

Materials and Methods: This retrospective study consecutively included 581 LDLT donors who donated right liver graft in 2013 (the development group, n = 207) and from 2014 to 2015 (the validation group, n = 374). Right liver graft volume was measured on CT using a software implemented with a deep learning algorithm. In the development group, volume-to-weight conversion formula was constructed by linear regression analysis between the CT-measured right liver graft volume and the intraoperatively measured graft weight. In the

validation group, the agreement between the estimated graft weights and measured graft weights was assessed using the 95% Bland-Altman limit-of-agreement (LOA).

Results: Mean process time for graft volume measurement on CT was 1.8 ± 0.6 minutes (range, 1.3 - 8.0 minutes). The volume-to-weight conversion formula constructed in the development group was as follows: estimated graft weight (g) = 206.3 + 0.653 x CT-measured right liver graft volume (ml) ($r = 0.878$, $p < .001$). In the validation group, the Bland Altman 95% LOA for the agreement between the estimated and the measured graft weights was -1.7% ± 17.1%.

Conclusions: The DLA-assisted CT volumetry allows for time-efficient and accurate estimation of graft weight estimation in LDLT. The measurement error of CT volumetric estimation of right liver graft weight is approximately 17% of measured graft weight.

Keywords: Deep learning; CT volumetry; Segmentation; Living right liver donors

목차

표 및 그림 차례

서론

Living donor liver transplantation (LDLT) is an effective therapeutic option for patients with end-stage liver disease (1). Adequate graft mass is one of major components for successful LDLT. The use of small-for-size grafts with graft-to-recipient weight ratios less than 0.8 to 1% is known to be associated with graft malfunction, while an insufficient remnant liver mass after harvesting graft may threaten donor's safety (2, 3). Therefore, an accurate preoperative estimation of graft weight is a prerequisite step in LDLT to ensure the safety of both recipients and donors.

Computed tomography (CT) volumetry has been widely used for preoperative graft volume measurement in LDLT (4-12), and graft weight is usually estimated using CT-measured right liver graft volume and volume-to-weight conversion formula (10-15). Although there have been a few prior studies which assessed the performance of CT volumetry in graft weight estimation (5, 7, 8, 10-17), these studies had limitations. The volume-to-weight conversion formulae used in the previous studies were not reliable since they were derived from a small study population (i.e., $\leq$ 16 subjects) (10, 11, 14), pathologic liver conditions (10) or the assumption of the same density of liver and water (13, 15, 18), which may have led to a biased estimation of graft weight. The previous studies assessed the correlations or mean differences between the estimated and actual graft weights but did not evaluate the measurement error of CT volumetric graft weight estimation (5-12), which would be important to predict the range of actual graft weight in individual LDLT donors.

One obstacle that limits the clinical use of CT volumetry has been time-consuming organ segmentation process. Recently, deep learning has been emerged as a method for automated image analysis. Recent studies demonstrated that a deep learning algorithm (DLA) enabled fully automated segmentation of the liver using CT images with a high accuracy, allowing for automated liver volume measurement without user interaction (19). Thus, the application of DLA for CT-based liver segmentation would dramatically improve time-efficiency of CT volumetry in estimating graft weight for LDLT.

Therefore, the purpose of our study was to construct graft volume-to-weight conversion formula and to evaluate the accuracy of DLA-assisted CT volumetric estimation of right liver graft weight in a large cohort of living liver donors who donated right liver graft.

As far as we know, this is the first study of fully automated DLA assisted CT volumetric estimation of right liver graft weight in LDLT.

연구대상 및 연구방법

This retrospective study was approved by our institutional review board, which waived the requirement for patients' informed consent.

Study population

We retrospectively and consecutively enrolled living liver donors who donated right liver graft from 2013 to 2015 in our institution. Eligible donors were those who had CT examination within three months prior to liver donation and those who had intra-operative graft weight measurement. A total of 581 donors satisfied the eligibility criteria and comprised the study population (Fig 1). The study population was, then, divided into the development group (liver donation in 2013, n = 207) and the validation group (liver donation from 2014 to 2015, n = 374). A subset of 50 donors who were randomly selected from 소 e validation group comprised the subgroup for assessing inter-reader agreement in graft volume measurement.

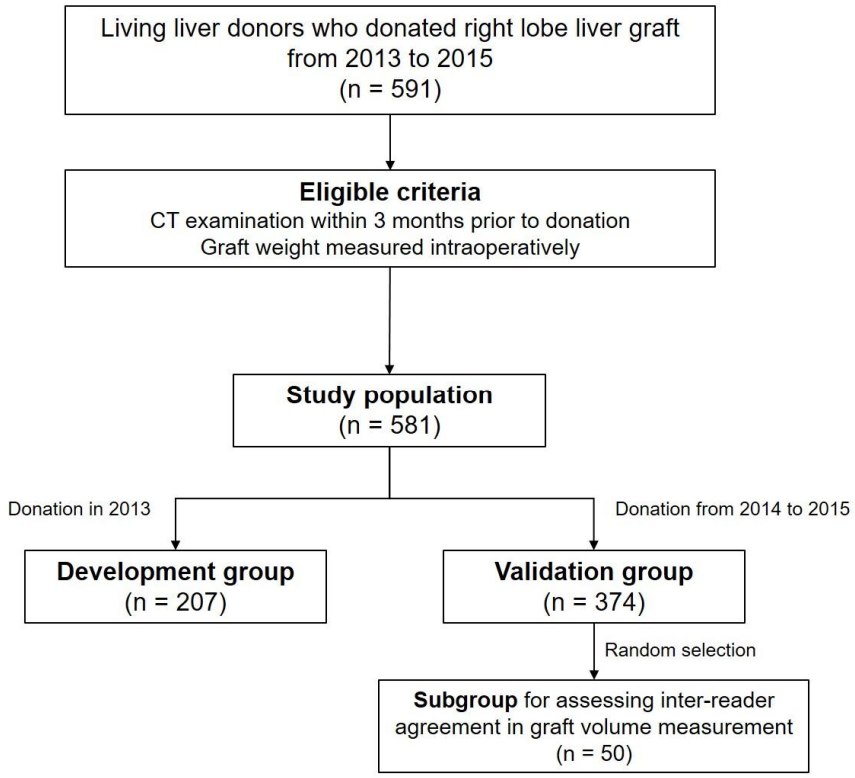

Figure 1. Flow diagram of the study population

CT examination

CT examinations were performed using various CT scanners and techniques; detailed information is presented in the supplementary table 1. CT scans were obtained using 16-channel (Sensation 16, Simens Healthineers, Erlangen, Germany), 64-channel (Definition AS, Siemens Healthineers or Lightspeed VCT, GE Healthcare, Milwaukee, WI, USA), or 128-channel (Definition Flash, Siemens Healthineers) or scanners. Portal venous phase images were obtained 76 seconds after intravenous contrast administration with tube voltages of 100 or 120 kVp, tube currents of 200-440 mA with an automatic exposure control, and section thickness of 3- or 5-mm with no gap.

CT techniques (N, %)	Total	Developmental group	Validation group
No. of patients	581	207	374
CT detector configuration			
16 channels	105 (18.1%)	58 (28.0%)	47 (12.6%)
64 channels	62 (10.7%)	21 (10.1%)	41 (11.0%)
128 channels	414 (71.3%)	128 (61.8%)	286 (76.5%)
Tube voltage			
100 kVp	573 (98.6%)	206 (99.5%)	367 (98.1%)
120 kVp	8 (1.4%)	1 (0.5%)	7 (1.9%)
Slice thickness			
3 mm	25 (4.3%)	3 (1.4%)	22 (5.9%)
5 mm	556 (95.7%)	204 (98.6%)	352 (94.1%)
CT vendors			
GE	7 (1.2%)	0 (0.0%)	7 (1.9%)
Siemens	574 (98.8%)	207 (100.0%)	367 (98.1%)

Table 1 CT imaging techniques used for development and validation group

Graft volume measurement using a deep learning algorithm for liver segmentation

Graft volume was measured by one third-year radiology resident (P.R.) on portal venous phase CT images. In the beginning of CT review, the reader analyzed the CT data of

the first 30 donors in the development group together with an experienced radiologist (L.S.S. with 23-year experience of abdominal imaging) for a training purpose. The CT data was analyzed using the software (GoCDSS; SmartCareworks Inc., Seoul, Korea) that was implemented with a deep learning algorithm (DLA) for automated liver segmentation. The detailed information of the DLA was described in a separate technical publication (19). Briefly, the algorithm performs whole liver segmentation excluding large hepatic vessels with a dice similarity score of 97% in a computation time of 33 seconds for a typical abdominal CT examination (19). Upon uploading the CT data, the software automatically performed liver segmentation. Then, the reader reviewed CT images along with the deep learning-generated liver segmentation results and corrected any segmentation errors. The reader defined the resection plane for the right liver graft based on the Cantlie line by drawing the two dividing lines (one along the main axis of the middle hepatic vein superiorly and the other along the imaginary line between the gallbladder and inferior vena cava inferiorly) on the selected images (Fig 2). The software completed the resection plane by interpolation of the two dividing lines. The volumes of the whole liver and the right liver liver graft were automatically calculated by summation of area multiplied by slice interval. The times required for reviewing CT images, correcting segmentation errors, and defining resection plane were recorded. In the subset of 50 donors in the validation group, the second reader (L.S.S) independently measured graft volume for assessing inter-reader agreement in graft volume measurement.

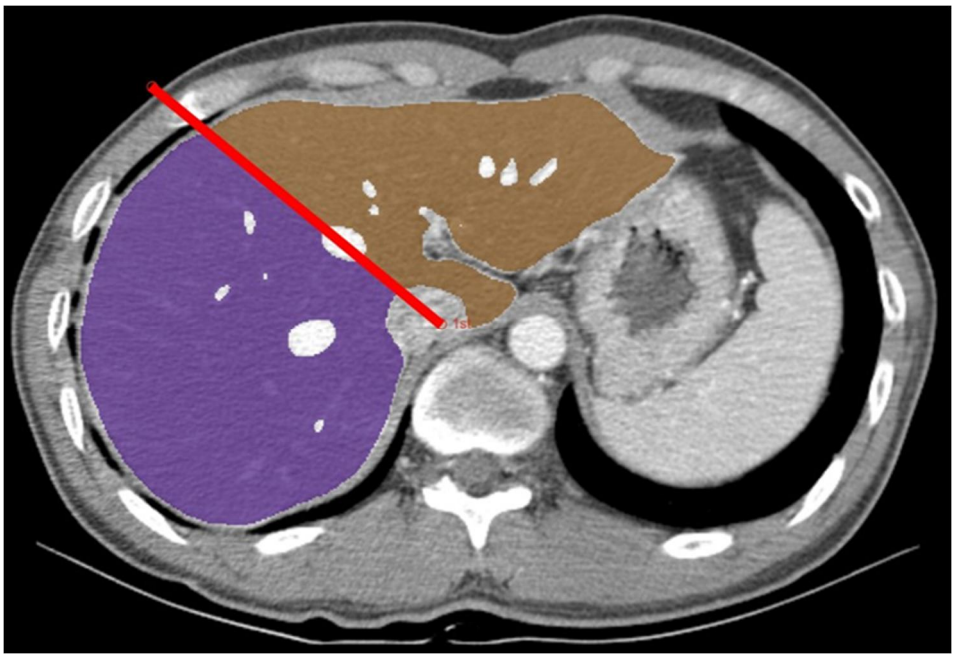

Figure 2 – Right liver graft volume measurement using deep learning algorithm-assisted CT volumetry. An axial portal venous phase CT image in a 44-year-old male donor was overlaid with right liver mask (purple), left lobe mask (brown), and a dividing line (red line). CT image data were first processed by the deep learning algorithm for whole liver segmentation. The radiologist reviewed deep learning generated liver segmentation results, corrected any error in segmentation, and defined the resection plane for the right liver graft by drawing the dividing lines.

Clinical and pathologic data and intraoperative graft weight measurement

Clinical data including age, sex, height, weight, and body mass index were obtained on the day of CT examinations. The degree of hepatic steatosis (HS) was assessed by pathologic analysis of US-guided percutaneous liver biopsy specimen that was performed 1-78 days (median, 17 days) prior to liver donation as a part of donor work-up. The degree of HS was graded as none (<5%), mild (5-33%), moderate (34-66%), or severe (>66%) as defined by the non-alcoholic steatohepatitis Clinical Research Network scoring system (20). Graft weight that is measured during the donor hepatectomy served as the reference standard in

our study. Donor hepatectomy was performed according to the procedure as described previously (5). Briefly, the demarcation line of the right liver is drawn based on the color change of the liver surface that occurred during temporary atraumatic clamping of the right portal vein and right hepatic artery. Parenchymal dissection was performed with the middle hepatic vein as the anatomic landmark, i.e., along the right (graft without middle hepatic vein) or left (graft with middle hepatic vein) side of the middle hepatic vein. Dissection of dorsal part of the liver were perform using a hanging maneuver that allows transecting the liver parenchyma down to the inferior vena cava. After harvesting a right liver graft, the surgeons shook the excised graft to spill out the remaining blood, waited for a few seconds for natural drainage, and then measured the blood-free graft weight using an electronic laboratory scale (FD 110; Excel Precision, Jiangsu, China).

Statistical analysis

The characteristics of the development and the validation groups were compared using the independent t-test or the Fisher's exact test. Agreement between the whole liver volume automatically measured with deep learning and those measured after the radiologist's correction was evaluated using 95% Bland-Altman limits of agreement (LOA). The 95% Bland-Altman LOAs were expressed as a percentage of the measured values and as the mean difference ± 1.96 x standard deviation (SD) of the difference, where the mean difference represents systemic bias, and 1.96 x SD of the difference represents the measurement error. In developmental group, to evaluate the confounding effect of HS on the graft weight, the multivariable linear regression analysis was performed by including the HS and CT-measured right liver graft volume as independent variables and the graft weight as the dependent variable. Then, the formula to convert CT-measured right liver graft volume to graft weight was built using the univariable linear regression analysis. In the validation group, the graft weight was estimated using CT-measured right liver graft volume and the conversion formula derived from the development group. Then, the agreement between the estimated and actual graft weights was assessed using the concordance correlation coefficient (CCC) and the 95% Bland-Altman LOA. In the subgroup including 50 donors in the validation group, the inter-reader agreement between the graft volumes measured by the

two radiologists was assessed using the CCC and the 95% Bland-Altman LOA. To assess the factors influencing the magnitude of error in graft weight estimation, multivariable linear regression analysis was performed in the validation cohort, including the age, sex, BMI, HS, interval between CT scan and liver donation, and type of liver graft (right liver graft with or without middle hepatic vein) as independent variables and the percentage difference between the estimated and measured graft weight, i.e., (estimated graft weight – actual graft weight)/actual graft weight, as the dependent variable. Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA) and MedCalc software version 14.8.1 (MedCalc, Ostend, Belgium). P values less than 0 .05 were considered to indicate significant differences.

연구결과

Characteristics of study population

Table 2 summarizes the characteristics of the study population. The study population included 581 donors (413 men and 168 women; mean age, 27.7 years; age range, 17-54 years).. Most donors had non-steatotic liver, and clinically relevant HS was present in 89 (15.3%) donors, with mild HS in 87 (15.0%) and moderate HS in two (0.3%). The development and validation groups included 207 (132 men and 75 women; mean age, 27.6 years; age range, 18-54 years) and 374 (281 men and 93 women; mean age, 27.8 years; age range, 17-52 years) donors, respectively. The developmental group and validation group showed significant differences in sex (P =.004), BMI (P = .015), body weight (P = .022) and intraoperatively measured graft weight (P=.004).

Table 2. Characteristics of the study population

	Total	Developmental group	Validation group	P-value*
No. of patients	581	207	374	
Age (years, mean ± SD)	27.7±7.2	27.6±6.9	27.8±7.3	0.661
Sex				
Male (N, %)	413 (71.1)	132 (63.8)	282 (74.8)	0.004
Hepatic steatosis (N, %)				0.816
None	492 (84.7)	177 (85.5)	315 (84.2)	
Mild	87 (15.0)	29 (14.0)	58 (15.5)	
Moderate	2 (0.3)	1 (0.5)	1 (0.3)	
BMI (kg/m², mean ± SD)	22.9±2.9	22.5±2.9	23.1±2.9	0.015
Height (cm, mean ± SD)	170.4±8.1	169.9±8.4	170.7±7.9	0.268
Weight (kg, mean ± SD)	66.8±11.4	65.4±11.7	67.6±11.1	0.022
Type of RLG (N, %) RLG without MHV RLG with MHV	 559/96.2 22/3.8	 196/94.7 11/5.3	 363/97.1 11/2.9	0.151
Interval between CT scan and donation (days, mean± SD)	30.6±19.0	30.9±18.8	30.4±19.1	0.728
Graft weight (g, mean ± SD)	748.8±129.3	728.1±123.5	760.2±131.2	0.004

*P-values were obtained from the comparison between the development and validation groups

RLG = right liver graft; MHV = middle hepatic vein.

Whole liver segmentation and right liver graft volume estimation using DLA

Deep learning-generated automated segmentation of whole liver was found to have a segmentation error that required radiologists' correction in 166 (28.6%) donors. Most segmentation errors were minor and were associated with a short correction time (the mean time required for radiologists' correction ± standard deviation [SD], 12.8 ± 33.6 seconds) and a small change in volume (95% Bland and Altman LOAs, 0.05% ± 3.0% of measured liver volume). The mean process time, including the review and correction of deep learning-generated segmentation and the division of the segmented liver, was 1.8 ± 0.6 minutes (range, 1.3 - 8.0 minutes).

Construction of graft volume-to-weight conversion formula in the development group

In the development group, the CT-measured right liver graft volume and the graft weight measured during donor hepatectomy ranged from 767.8 to 1880.7 mL (mean ± SD, 1249.0±237.9) and from 420.0 to 1025.0 g (mean ± SD, 728.1±123.5), respectively. At multivariable linear regression analysis, HS did not have significant effect on graft weight (coefficient, -0.34; P = .667) after accounting for the effect of graft volume on graft weight (coefficient, 0.655; P <.001). Therefore, we constructed the formula to convert CT-measured right liver graft volume to graft weight in the entire development group without excluding donors with HS (Fig. 3). The conversion formula was as follows: estimated graft weight (g) = 206.3 + 0.653 x CT-measured right liver graft volume (ml) ($r = 0.878$, $p < .001$).

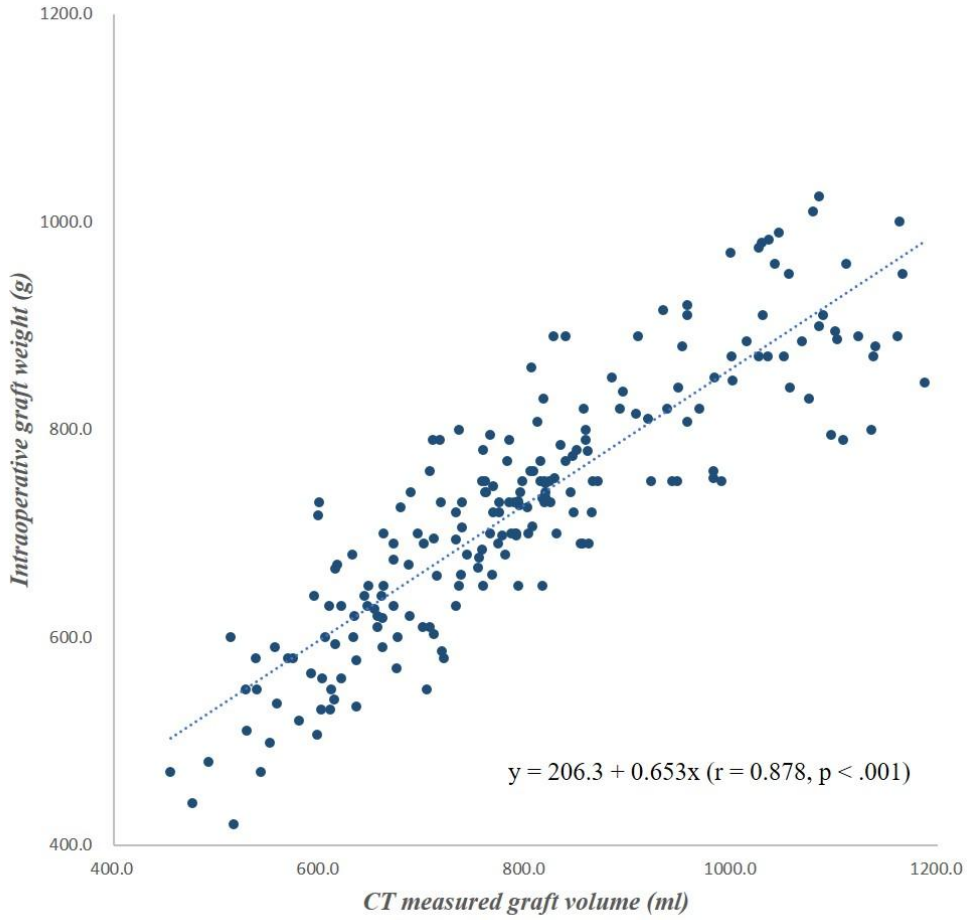

Figure 3 – Scatter plot of the CT-measured right liver graft volume versus intraoperative graft weight in the development group. Solid line indicates best-fit regression line. The regression equation obtained using the linear regression analysis was presented.

Agreement between the estimated and the measured graft weights in the validation group

In the validation group, CT-measured right liver graft volume, estimated graft weight, and intraoperatively measured graft weight ranged from 722.9 to 2259.6 mL (mean ± SD, 1281.9±233.4), from 520.0 to 1153.7 g (mean ± SD, 743.6±104.0), and from 456.0 to 1400.0 g (mean ± SD, 760.2±131.2), respectively. The CCC for the agreement between the

estimated and the measured graft weights was 0.834 (95% confidence interval [CI], 0.804 to 0.860) (Fig. 4). The Bland Altman 95% LOA was -1.7% ± 17.1% (P = .002 for the difference of mean bias from zero), indicating the mean bias of -1.7% and the measurement error of 17.1% of measured graft weight (Fig. 5).

Inter-reader agreement in graft volume measurement was assessed in the subset of 50 donors in the validation cohort. The CCC for the agreement between the graft volumes measured by the two readers was 0.998 (95% CI, 0.996-0.999), and the Bland Altman 95% LOA was 0.2% ± 1.8% (P = .069).

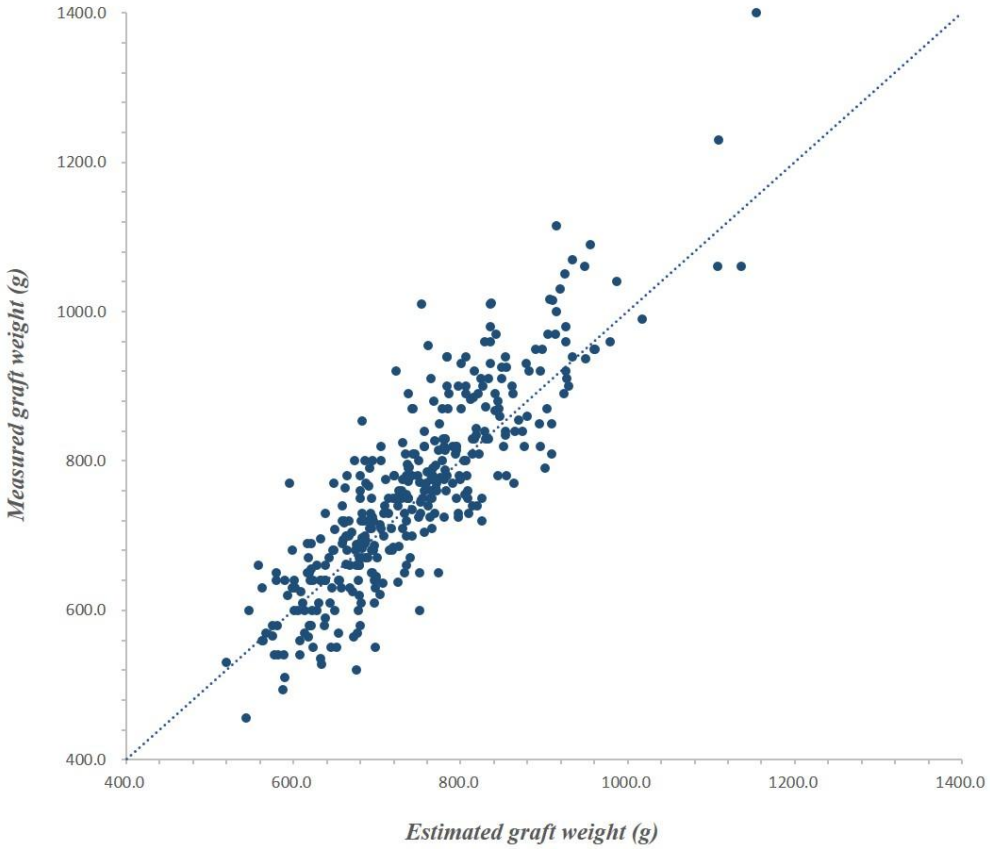

Figure 4. Scatter plot of the estimated and measured graft weights in the validation group. Dashed line is the reference line indicating complete agreement. The concordance correlation coefficient between the estimated and measured graft weights was 0.834 (95% confidence interval, 0.804 to 0.860, p<0.001)

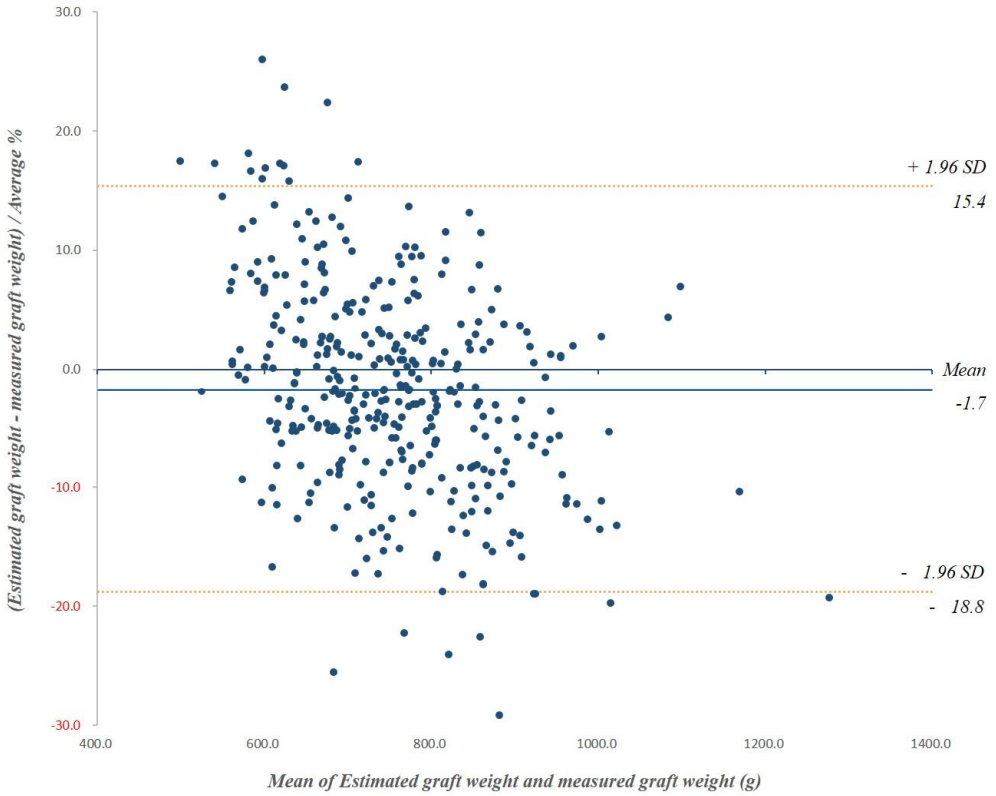

Figure 5 – The Bland Altman plot for the agreement between the estimated and measured right liver graft weights in the validation group. Solid line indicates mean difference and dashed lines indicate upper and lower limits of 95% limits of agreement. The Bland Altman 95% LOA was -1.7% ± 17.1% (P = .002 for the difference of mean bias from zero). SD = standard deviation

Factors associated with the difference in the estimated and measured graft weights

In the validation cohort, multivariable linear regression analysis revealed that the sex (coefficient, -1.73; P = .001) and BMI (coefficient, -0.2; P < .001) have significant independent association with the percentage difference between the estimated and measured graft weight, while age (P = .076), the degree of HS (P = .577), interval between CT and liver donation (P = .111), and type of liver graft (P = .279) did not. The Bland Altman 95% LOA between the estimated and measured graft weights were -2.6% ± 16.8% (P < .001) and 0.9% ± 16.8% (P = .306) for men and women, respectively. When donors were sub-grouped using BMI, the Bland Altman 95% LOA between the estimated and measured graft weights

were -1.3% ± 16.2% (P =.009) and -4.2% ± 17.0% (P <.001) for the donors with BMI < 25 kg/m² and the overweight or obese donors with BMI ≥ 25 kg/m², respectively.

고찰

Our study evaluated the efficiency and accuracy of CT volumetry using a deep learning algorithm for the preoperative estimation of right-lobe graft weight in living donor liver transplantation. We found that the DLA allowed for a time-efficient measurement of graft volume on CT. The CT data analysis with the DLA was performed as a background process so that the reader reviewed CT images with DLA-generated liver segmentation results. The DLA enabled highly accurate segmentation of the liver. The DLA-generated liver segmentation results did not require additional correction in an approximately 70% of the donors, and minor segmentation errors, which could be rapidly correct by the reviewing radiologist, were observed in only 30% of donors. As a result, CT volumetric assessment of right-lobe graft could be rapidly performed in an average process time of 1.8 minutes.

We developed the graft volume-to-weight conversion formula in a large number of donors (i.e., 207 donors) in the development group. In the validation group, graft weights estimated using the CT-measured right liver graft volume and the conversion formula showed an overall good agreement with the measured graft weights (i.e., CCC of 0.834). The Bland Altman 95% LOA indicated the measurement error of ± 17.1% of graft weight, which encompasses the 95-percentile range of the difference between the estimated and measured graft weights. This can be used in clinical practice to predict the range of actual graft weight based on the estimated graft weight using CT volumetry. Though the measurement error in our study appears large, the previous studies reported even greater difference between the estimated and measured graft weights ranging from -48.2% to 66.2% (5, 8, 12) than our study. As suggested by previous studies, multiple factors may have contributed to the error in CT volumetric estimation of graft weight, including mismatch between expected and actual resection plane (6, 12), graft dehydration (7, 12), and variable amount of blood remained in the graft (8).

Our validation result showed a small but significant bias in the estimated graft weights, indicating that graft weight was underestimated by 1.7% in the validation group. The mean bias of 1.7% in our study was smaller than those reported in the previous studies (i.e., -9.8% to 2.4% of graft weight) (5, 8), which may have been partly owing to the use of conversion formula developed in a larger study population in our study. Though not fully

understood, we speculate that the bias in the estimated graft weights in the validation group may have been related with different characteristics between the development and validation groups. Our study showed that sex and BMI were significant factors associated with the percentage difference between the estimated and measured graft weight toward an underestimation of graft weight in men and in donors with higher BMI. Thus, a significantly higher proportion of men and higher BMI in the validation group compared with the development group, may have led to a small underestimation of graft weight in the validation group.

We found a nearly perfect interobserver agreement (i.e., CCC of 0.998; Bland Altman 95% LOA of -1.6% to 2.0% of measured volume) in graft volume measurement between the two readers. This finding is noteworthy, given different experience between the two readers (i.e., third-year radiology residence vs. abdominal radiologist with 23-year experience). We assume that the use of automated liver segmentation with the DLA may help reduce inter-reader variability in liver segmentation, making CT-based graft volume measurement simple enough for a less experienced reader to learn after a short training session.

In our study, HS did not have significant confounding effect on the association between CT-measured right liver graft volume and intraoperative graft weight in the development cohort. In addition, the degree of HS was not significant factor associated with the percentage difference between the estimated and measured graft weights. However, this finding should be interpreted with caution, given the fact that most donors in our study population had no or mild HS. Despite some controversies, there have been a few prior reports suggesting that HS is associated with an increase in liver volume (21-23). Therefore, our results may not be directly generalizable to donors with moderate to severe HS.

Our study had limitations. First, retrospective design may be subject to a selection bias and bias from missing data, despite our efforts to minimize such biases by enrolling consecutive donors. Second, we evaluated only right liver graft in our study since that right liver graft is the preferred graft for LDLT to meet recipients' metabolic demand (24, 25). The measurement error range for CT volumetric graft weight estimation shown in our study may not be directly applicable to other types of liver graft. Finally, the

development and validation groups in our study were enrolled in the same institution. An external validation in a completely different population may have provided more conclusive validation results.

결론

In conclusion, we proposed a graft volume-to-weight conversion formula that would be useful for pre-operative CT volumetric estimation of graft weight in LDLT. The DLA-assisted CT volumetry allows for time-efficient and accurate estimation of graft weight estimation in LDLT. The measurement error of CT volumetric estimation of right liver graft weight is approximately 17% of measured graft weight.

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국문요약

연구제목: 생체 우측 간이식 기증 대규모 코호트에서 딥러닝 보조 CT volumetry를 이용한 우측 간 이식편의 무게 예측의 정확도 및 효율성

연구배경: CT volumetry은 생체 간이식 시 이식편의 무게 추정에 널리 사용되어 왔으며, 최근 딥러닝을 통한 자동 간 분할이 가능해지면서 그 효율성이 향상되었다. 그러나 이식편의 무게 예측에 대한 CT volumetry의 정확도는 아직 잘 알려지지 않았다. 따라서 우리는 이 연구를 통해 생체 우측 간이식 기증 대규모 코호트에서 딥러닝 보조 CT volumetry의 우측 간의 무게 예측의 정확도 및 효율성을 확인하고자 한다.

연구방법: 본 후향적 연구는 2013년~2015년 동안 본원에서 생체 우엽 간 기증을 시행한 환자군을 대상으로 하였으며, 이들은 기증 연도를 기준으로 발달군(2013년 기증)과 검증군(2014년~2015년 기증)으로 나뉘었다. 딥러닝 보조 소프트웨어를 이용하여 우측 간 이식편의 부피를 측정하였고, 발달군에서 CT 측정 우측 간 이식편의 부피와 수술장에서 측정한 이식편의 무게를 이용하여 회귀분석을 통해 이식편 부피-무게 변환 공식을 도출하였다. 검증군에서 앞서 도출된 공식에 대입하여 구한 이식편의 예측 무게와 수술장에서 측정한 이식편의 무게 사이의 일치도를 Concordance correlation coefficient (CCC)와 95% Bland-Altman limits-of-agreement (LOA) 이용하여 평가하였다.

연구결과: CT에서 우측 간 이식편의 부피 측정을 위한 평균 소요시간은 1.8±0.6분 (범위 1.3~8.0분)이었다. 발달군에서 도출된 우측 간 이식편의 부피-무게 변환 공식은 다음과 같다. 우측 간 이식편 예측 무게 (g) = 206.3 + 0.653 x CT 측정 우측 간 이식편 부피(ml) ($r = 0.878$, $p < .001$). 검증군에서 우측 간 이식편 예측 무게와 수술장 측정 무게 사이의 일치도는 Bland Altman 95% LOA -1.7% ± 17.1% ($p = .002$)로 확인되었다.

연구결론: 딥러닝 보조 CT volumetry은 생체 간이식에서 수술 전 우측 간 이식편의 무게 예측에 있어 매우 시간 효율적이며, 정확한 측정을 가능하게 한다. CT

volumetry의 우측 간 이식편의 무게 예측의 오차 범위는 이식편 무게의 약 17% 이내였다.