Objective evaluation of laparoscopic surgical skills in wet lab training based on motion analysis and machine learning

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Abstract
Background Our aim was to build a skill assessment system, providing objective feedback to trainees based on the motion metrics of laparoscopic surgical instruments.

Methods Participants performed tissue dissection around the aorta (tissue dissection task) and renal parenchymal closure (parenchymal-suturing task), using swine organs in a box trainer under a motion capture (Mocap) system. Two experts assessed the recorded movies, according to the formula of global operative assessment of laparoscopic skills (GOALS: score range, 5–25), and the mean scores were utilized as objective variables in the regression analyses. The correlations between mean GOALS scores and Mocap metrics were evaluated, and potential Mocap metrics with a Spearman’s rank correlation coefficient value exceeding 0.4 were selected for each GOALS item estimation. Four regression algorithms, support vector regression (SVR), principal component analysis (PCA)-SVR, ridge regression, and partial least squares regression, were utilized for automatic GOALS estimation. Model validation was conducted by nested and repeated k-fold cross validation, and the mean absolute error (MAE) was calculated to evaluate the accuracy of each regression model.

Results Forty-five urologic, 9 gastroenterological, and 3 gynecologic surgeons, 4 junior residents, and 9 medical students participated in the training. In both tasks, a positive correlation was observed between the speed-related parameters (e.g., velocity, velocity range, acceleration, jerk) and mean GOALS scores, with a negative correlation between the efficiency-related parameters (e.g., task time, path length, number of opening/closing operations) and mean GOALS scores. Among the 4 algorithms, SVR showed the highest accuracy in the tissue dissection task (MAE\text{median} = 2.2352), and PCA-SVR in the parenchymal-suturing task (MAE\text{median} = 1.2714), based on 100 iterations of the validation process of automatic GOALS estimation.

Conclusion We developed a machine learning–based GOALS scoring system in wet lab training, with an error of approximately 1–2 points for the total score, and motion metrics that were explainable to trainees. Our future challenges are the further improvement of onsite GOALS feedback, exploring the educational benefit of our model and building an efficient training program.

Keywords Laparoscopic surgery · Simulation training · Motion capture · Machine learning · Surgical education

Introduction

Due to the widespread dissemination of minimally invasive surgery such as laparoscopic and robotic surgeries that require specific psychomotor skills, working hour restrictions, and ethical consideration regarding patient safety, simulation training outside the operating theater has been utilized in a broad range of surgical disciplines. In order to practice essential laparoscopic surgical skills, we also...
utilized simulation training using cadaveric porcine organs, including tissue dissection around the aorta, applying a Hem-o-lok in the vascular pedicle, and renal parenchymal closure, and reported its good construct validity [1]. Recently, we developed a novel motion capture (Mocap) system that could recognize each surgical instrument individually irrespective of instrument exchanges [2], and identified the motion characteristics of multiple surgical instruments according to the level of surgical experiences in a series of our aforementioned wet lab training. For example, in a task of tissue dissection around the swine aorta named “Task 1”, a shorter path length and faster velocity/acceleration/jerk were observed for both scissors and a Hem-o-lok applier in experts (> 50 laparoscopic surgeries), and especially in experts with > 100 cases, scissors moved more frequently in the close zone (0 < to < 2 cm from aorta) than in those with 50–99 cases [3].

Our goals are to characterize experts’ psychomotor skills based on motion metrics of surgical instruments, further improve surgical skills, and promote patient safety. As the next step, in order to enrich laparoscopic training programs, we aim to build a machine learning–based skill assessment system, in which the skill level is automatically evaluated and trainees receive explainable feedback based on the Mocap metrics of surgical instruments. In brief, two experts watched the recorded movies and evaluated the surgical dexterity according to the formula of global operative assessment of laparoscopic skills (GOALS) [4]. Using the mean GOALS scores as training data, we developed a machine learning–based GOALS scoring system in wet lab training, which could mitigate the educators’ workload, and promote self-training and peer-learning opportunities.

Materials and methods

The institutional review board approved the present study (No. 018–0257). We previously reported the initial results based on the present Mocap system among urologic surgeons, a junior resident, and medical students (first data collection: n = 45, from December 2018 to February 2019) [3]. We continued data collection, including general and gynecologic surgeons (second data collection: from the end of May 2019 to September 2019). In the second data collection, participants performed tissue dissection around a swine aorta (task 1), and needle driving and making knots on kidney parenchyma (task 3), while only needle driving on kidney parenchyma (task 2) was not included because the characteristics of motion metrics divided by the level of surgical experiences were almost the same between tasks 2 and 3 in the first data collection [3]. Overall, a total of 70 participants performed 89 training sessions of tasks 1 and 3 during the whole study period (19 participants overlapped during the first and second data collections). Written informed consent was obtained regarding the use of their data for research.

We previously reported the details of the present training tasks [3]. Briefly, swine cadaveric organs were set in a box trainer (Endowork ProI®, Kyoto Kagaku, Japan). During the training, one of the 4 authors (TA, MH, JF, and NI) performed the role of a scopist, using a video system (VISERA Pro Video System Center OTV-S7Pro, Olympus, Japan). In task 1, participants were asked to dissect tissues around the aorta, dividing encountered mesenteric vessels after applying a Hem-o-lok clip. In task 3, using a 15-cm 2–0 CT-1 VICRYL® thread, participants were required to complete three square single-throw knots at 2 different sites on a kidney. If participants had trouble with the simulation, the scopist verbally guided each step of the task. All training sessions were video-recorded for later analyses. Demographic data and experience of laparoscopic surgeries were collected after the training session. The subjective mental workload was assessed by NASA Task Load Index after each training session for subsequent analysis.

Motion capture analysis

We previously reported the details of the present Mocap system [3]. Briefly, the Mocap system, which consists of 6 infrared cameras (OptiTrack Prime 41, NaturalPoint Inc., USA), simultaneously tracked multiple surgical instruments. Infrared reflective marker sets with a different arrangement pattern were attached to handles of each surgical device, which enabled our system to recognize each instrument individually regardless of the exchanges of instruments. The tip trajectories were calculated based on the positional relationship between the tip and handle. The track of the tip of a device (x_i, y_i, and z_i) was smoothed via the Savitzky-Golay filter [5], and its derivatives \( \frac{dx_i}{dt} \), \( \frac{dy_i}{dt} \), and \( \frac{dz_i}{dt} \) (j = 1 to 3) were also calculated by the filter. The definitions of measurement outcomes (Mocap metrics) are summarized in Supplementary Table 1. In the second data collection, grasping forces with strain gauges were utilized in task 1 in order to measure the grasping force and position of grasping forces, although it was not a focus of the present study. Figure 1 shows pictures of the Mocap system, a surgical instrument with infrared markers, and endoscopic views of training tasks.

Analyses and statistics

Two experts (TA and KH) evaluated the recorded movies in accordance with the GOALS formula [4]. Both raters performed more than 500 laparoscopic surgeries, and they were familiar with GOALS assessment because they were involved in the original validation study of the present wet
Anonymous video recordings were given to the two experts, and they independently scored the movies without any discussion or knowledge of participants’ backgrounds. The mean scores were utilized for subsequent analysis. The correlation was also evaluated by Spearman’s rank correlation coefficient. Next, correlations between mean GOALS scores and Mocap metrics were evaluated. For the subsequent machine learning analyses in order to develop an automatic skill assessment system according to the formula of GOALS, suitable Mocap metrics with a coefficient absolute value of more than 0.4 were selected for each GOALS item estimation based on the two authors’ discussions (KE and TA). Supplementary Table 2 summarizes the hypothesis for each item’s estimation, derived from the discussion process. In task 3, the score of “Tissue handling” was omitted because needle and thread manipulations were the main components of this drill.

In order to establish automatic GOALS assessment, we utilized the four regression algorithms: support vector regression (SVR), principal component analysis (PCA)-SVR, ridge regression (RR), and partial least squares regression (PLSR). Each algorithm has hyperparameters that must be determined before building a model. In this study, a grid search is performed to identify the best combination of parameters. The details of these algorithms and candidate parameters for the grid search are shown in Supplementary Table 3.

All Mocap metrics were normalized using robust Z-score normalization before inputting for these regression algorithms. The robust Z score, \( z_i \), for data, \( x_i \), can be calculated as follows:

\[
    z_i = \frac{x_i - x_m}{\text{NIQR}}
\]

Here, \( x_m \) is the median for data \( x \), and \( \text{NIQR} \) is the normalized interquartile range, calculated as \( \text{NIQR} = 0.7414 \cdot \text{IQR} \) (\( \text{IQR} \)=interquartile range).

In order to evaluate the accuracies of each regression model, the mean absolute error (MAE) was used. MAE is calculated as follows:

\[
    \text{MAE} = \frac{1}{n} \sum_{i=1}^{n} |y_i - \hat{y}_i|,
\]

where \( n \) is the number of subjects, \( y_i \) is an actual GOALS score of subject \( i \), and \( \hat{y}_i \) is that predicted.

Model validation was conducted by nested and repeated k-fold cross-validation, a combined method of nested k-fold cross-validation and repeated cross-validation. Supplementary Fig. 1 shows the data flow of the validation process.
this validation method, nested k-fold cross-validation was repeated with different dataset divisions. The number of repetitions was set to 100 times in this study.

Spearman’s rank correlation coefficient was calculated using pandas ver. 1.1.4, data analysis library for Python (version 3.8.6.) [6]. All procedures of machine learning (parameter tuning, training, and validation models) were conducted using Scikit-learn, the machine learning library of Python [7]. The accuracies of each machine learning model calculated in the validation process were compared by the Kruskal–Wallis test. The Mann–Whitney U test was also utilized to assess the differences in model accuracy of each pair. Kruskal–Wallis and Mann–Whitney U tests were performed using JMP 14 (SAS, Japan).

Results

Table 1 shows a summary of participants’ backgrounds. Forty-five urologic surgeons, 9 gastroenterological surgeons, 3 gynecologic surgeons, 4 junior residents, and 9 medical students voluntarily participated in the training during the study period. Previous experiences of laparoscopic surgery were as follows: 0–9: n = 20, 10–49: n = 18, 50–99: n = 7, 100–499: n = 18, ≥ 500: n = 7. As described above, 19 joined the training multiple times, which resulted in a total of 89 training sessions. Due to video recording failure (task 1: n = 1 and task 3: n = 5), 88 movies of task 1 and 84 movies of task 3 were available for subsequent analyses.

Supplementary Fig. 2 shows scatterplots of GOALS scores assessed by the two experts. Good interrater correlations of GOALS scores were confirmed in both tasks 1 and 3 (Spearman’s rank correlation coefficient: task 1 = 0.7773, task 3 = 0.878). As shown in Supplementary Table 4, a good correlation was also confirmed in each component (coefficient: 0.6662–0.8443).

Figure 2 (a: task 1, b: task 3) shows a heatmap of Spearman’s correlation coefficients between Mocap metrics and the mean GOALS scores (each item and total). In both tasks, a positive correlation was observed between the speed-related parameters (e.g., velocity, velocity range, acceleration, jerk) and mean GOALS scores, with a negative correlation between the efficiency-related parameters (e.g., task time, path length, number of opening/closing operations) and mean GOALS scores. In other words, Mocap analysis revealed that surgeons with high GOALS scores manipulated surgical instruments fast and dynamically, which resulted in greater efficiency.

Table 2 summarizes the correspondence between each GOALS item and the selected Mocap metrics with a coefficient of 0.4 or higher. For example, regarding depth perception in task 1, as summarized in Supplementary Table 2, because we hypothesized that metrics associated with movements along the sheath axis reflect depth perception, and “applying a Hem-o-lok clip on the vessel smoothly and quickly” strongly reflects a good spatial ability, we utilized the depth path length (DPL) and number of opening/closing operations for grasping forceps, DPL and depth velocity (DV) for scissor forceps, and all Mocap metrics with >0.4 coefficient for the clip applier in subsequent machine learning analyses for the automatic skill assessment system.

Figure 3 shows box plots of MAEs regarding the accuracy of estimated GOALS scores (total) under repeated and nested cross-validation in each machine learning model (SVR, PCA-SVR, RR, and PLSR). Table 3 also shows a summary of the tests results including each GOALS component. Regarding the total GOALS score, the SVR method showed the highest accuracy in task 1 (Fig. 3a), and PCA-SVR in task 3 (Fig. 3b). The medians of the model accuracy of the 100 iterations of the validation process were $\text{MAE}_{\text{median}} = 2.2352$ in task 1 (SVR), and $\text{MAE}_{\text{median}} = 1.2714$ in task 3 (PCA-SVR). Figure 4 shows scatter plots of actual and predicted GOALS scores derived from 100 iterations. In task 1 (SVR), the errors between actual and predicted scores were smaller in the participants with actual scores > 15, and small in all participants in task 3 (PCA-SVR).

Discussion

Using motion metrics of the instruments, several previous studies were aimed to measure surgical skills [8, 9], and machine learning showed good performance to classify laparoscopic surgeons according to previous surgical experience [10–13]. For example, Oropesa et al. compared three methods: linear discriminant analysis (LDA), SVM, and an
Adaptive neuro-fuzzy inference system (AN-FIS), to classify 42 participants according to previous surgical experience (>10 laparoscopic surgeries performed vs. <10) by leave-one-out cross-validation [12]. Instrument movements were captured in three box trainer tasks (peg grasping task, task that requires placing three elastic bands through their corresponding posts, and coordinated peg transfer task) by the TrEndo tracking system [10]. They observed that the mean accuracy of classification was 71% with LDA, 78.2% with SVM, and 71.7% with AN-FIS. Overall, previous researchers utilized simple training tasks such as “peg transfer”, “pattern cutting”, or “suturing”, which did not require the exchange of surgical instruments, utilized previous surgical experience as a surrogate marker of surgical competence, and focused on the differential accuracy of each machine learning model regarding surgical competency, not providing comprehensive feedback to trainees based on the movements of surgical instruments. Rather, in the present study, using relatively complex training tasks (task 1: tissue dissection around a swine aorta, task 3: renal parenchymal closure) for which we previously reported good construct validity [1], we aimed to develop a wet-lab training model that offered completely objective feedback to trainees according to the GOALS formula.

Because our prior study showed that the level of surgical experience was not always associated with surgical dexterity on Mocap-based evaluation, we reviewed the recorded movies, and scored those according to the GOALS formula. GOALS is an already validated and widely used assessment tool for grading laparoscopic surgical skills, and consists of five items: depth perception, bimanual dexterity, efficiency, tissue handling, and autonomy [4]. Each item is scored on a Likert scale between 1 and 5, which results in a total score between 5 and 25. As a result, we observed good interrater correlation between the two experts for the total score and for each item both in tasks 1 and 3 (Supplementary Fig. 2, and Supplementary Table 4), and the mean scores were utilized for subsequent analyses.

As the next step, we evaluated the correlation between the mean GOALS scores and Mocap metrics. In both tasks, a positive correlation was observed between the speed-related parameters (e.g., velocity, velocity range, acceleration, jerk) and mean GOALS scores, with a negative correlation between the efficiency-related parameters (e.g., task time, path length, number of opening/closing operations) and the mean GOALS scores. "DP", "BD", "E", "TH", and "A" are items of GOALS. DP = Depth perception, BD = bimanual dexterity, E = efficiency, TH = tissue handling, A = autonomy. The prefixes of each item in the figure ("G", "S", "H", "R", "L") are instruments. G = Grasping forceps, S = scissors forceps, C = clip applier, R = right needle holder, L = left needle holder. The suffixes of each item in the figure are Mocap parameters.

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As the next step, we evaluated the correlation between the mean GOALS scores and Mocap metrics. In both tasks, a
positive correlation was observed in the speed-related metrics (e.g., velocity, velocity range, acceleration, jerk), and a negative correlation in the efficiency-related metrics (e.g., task time, path length, number of opening/closing operations). Because we aimed to calculate each GOALS item’s score according to its original meaning, potential Mocap metrics were selected based on the two authors’ discussions, as summarized in Supplementary Table 2. For example, as described above, we utilized the depth path length (DPL) and number of opening/closing operations with grasping forceps (we hypothesized that poor depth perception results in failure to grasp tissues), DPL and depth velocity (DV) with scissor forceps, and all Mocap metrics with >0.4 coefficient with the clip applier regarding depth perception in task 1. Because we considered that “applying a Hem-o-lok clip on a pedicle smoothly” strongly reflected the skill of depth perception, all Mocap metrics with >0.4 coefficient with the clip applier were included. In task 3, after discussion, we discontinued “Tissue handling” calculation because the task consisted of needle and thread control, not tissue manipulation.

In the present study, we utilized the four major algorithms for automatic GOALS estimation. As SVR and PCA-SVR are non-linear regression methods, and RR and PLSR are linear regression methods, we aimed to utilize a variety of regression methods. Regarding the validation process, in general, “leave-one-out cross-validation” has a tendency whereby the generalization error often has high variance because the model is constructed by \([n-1]\) samples out of a total of \([n]\) samples, and the constructed models may be
### Table 3 Comparitive summary of automatic GOALS assessment among the 4 regression algorithms

| GOALS item       | Median of MAEs (interquartile range) | p value     |
|------------------|--------------------------------------|-------------|
|                  | SVR       | PCA-SVR     | RR         | PLSR       | Kruskal–Wallis test, SVR vs. PCA SVR | SVR vs. RR         | SVR vs. PLSR    | PCA-SVR vs. RR | PCA-SVR vs. PLSR | RR vs. PLSR |
|                  |           |             |            |            |                                |                 |              |               |                 |             |
| **Task 1**       |           |             |            |            |                                |                 |              |               |                 |             |
| Depth perception | 0.5083 (0.4963–0.5221) | 0.5509 (0.5363–0.5630) | 0.5630 (0.5578–0.5684) | 0.5912 (0.5807–0.6032) | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Bimanual dexterity | 0.5234 (0.5116–0.5377) | 0.5543 (0.5419–0.5673) | 0.4964 (0.4925–0.5028) | 0.5109 (0.5027–0.5205) | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Efficiency       | 0.4804 (0.4695–0.4943) | 0.5102 (0.4951–0.5228) | 0.4751 (0.4635–0.4871) | 0.5261 (0.5166–0.5414) | <0.0001 | <0.0001 | 0.0357 | <0.0001 | <0.0001 | <0.0001 |
| Tissue handing   | 0.6679 (0.6480–0.6816) | 0.6114 (0.5971–0.6232) | 0.6280 (0.6225–0.6371) | 0.6408 (0.6310–0.6510) | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Autonomy         | 0.5323 (0.5195–0.5456) | 0.5733 (0.5653–0.5861) | 0.5803 (0.5681–0.5926) | 0.6066 (0.5975–0.6133) | <0.0001 | <0.0001 | <0.0001 | 0.0259 | <0.0001 | <0.0001 |
| **Total**        | 2.2352 (2.2141–2.2753) | 2.3555 (2.3278–2.3868) | 2.4917 (2.4020–2.4385) | 2.4933 (2.4673–2.5134) | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **Task 3**       |           |             |            |            |                                |                 |              |               |                 |             |
| Depth perception | 0.3671 (0.3611–0.3740) | 0.3575 (0.3512–0.3631) | 0.4147 (0.4112–0.4184) | 0.4077 (0.4053–0.4110) | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Bimanual dexterity | 0.4430 (0.4318–0.4559) | 0.4575 (0.4435–0.4729) | 0.5318 (0.5265–0.5376) | 0.5152 (0.5096–0.5225) | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Efficiency       | 0.3843 (0.3748–0.4004) | 0.3642 (0.3546–0.3791) | 0.5127 (0.5042–0.5230) | 0.5203 (0.5136–0.5303) | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Autonomy         | 0.3853 (0.3758–0.3944) | 0.3696 (0.3620–0.3830) | 0.5326 (0.5279–0.5386) | 0.5153 (0.5103–0.5209) | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **Total**        | 1.3336 (1.3156–1.3554) | 1.2714 (1.2513–1.2879) | 1.8105 (1.8000–1.8248) | 1.7794 (1.7693–1.7945) | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
identical to each other and the same as models built from the entire training set, which may result in overfitting. For these reasons, we performed k-fold cross-validation. In addition, in order to optimize hyper parameters of a model while avoiding overfitting to the dataset, we utilized nested cross-validation by nesting k-fold cross-validation. Regarding the accuracy of the machine learning model, in general, MAE and root mean squared error (RMSE) are frequently utilized. Regarding RMSE, because it uses the square error for calculation, it might be strongly influenced by outliers. In the present study, aiming to evaluate the error equally among all data, we used MAE, which utilizes an absolute error value for accuracy estimation.

As presented in Fig. 3 and Table 3, the SVR method showed the highest accuracy in task 1, and PCA-SVR in task 3. The medians of the model accuracy of 100 iterations of the validation process were $\text{MAE}_{\text{median}} = 2.2352$ points in task 1 (SVR), and $\text{MAE}_{\text{median}} = 1.2714$ points in task 3 (PCA-SVR). In other words, the SVR model can estimate the GOALS score with an error of approximately 2.2 points in the range of GOALS scores of 5–25 in task 1, and PCA-SVR with an error of approximately 1.3 points in the range of GOALS scores of 4–20 in task 3. As shown in Fig. 4, the errors between actual and predicted scores were smaller in the participants with actual scores $>15$ in task 1, and small in all participants in task 3 (PCA-SVR). Our observations suggest that in task 1, automatic feedback is more reliable in better surgeons, while reliable in a range of surgeons in task 3, and both tasks should be included in training drills in order to provide accurate feedback to participants according to the GOALS formula. Our future challenge is further improvement for onsite GOALS feedback. A randomized control study, with the hypothesis that motion capture–based feedback enhances the initial phase of the learning curve, would be an interesting study to address the educational benefit of the current model. In addition, we consider that our automated GOALS score can be used as part of a skill credentialing system.

Limitations of this study include the small sample size, lack of qualitative assessment of the tissue dissection and intracorporeal knot suture themselves, and heterogeneity including, for example, three surgeons were left-handed, although they performed actual surgeries with a right-handed style. Regarding the accuracy of the tip position, we previously compared the tip position calculated by the positional relationship between the tip and handle, with the actual tip position, which was measured by tracking the marker attached to the tip of devices [2]. The positional errors were less than 2 mm, and the current smoothing process also might influence the metrics, although we consider the errors to be within an acceptable range.

In addition, the present study was never free from the uncertainty derived from human assessment of the GOALS score, although we utilized mean scores from two experts, who independently assessed the movies in a blind manner in order to mitigate human bias. The selection process of Mocap metrics for each GOALS item calculation was also not free from bias. As described above, in order to mitigate the risk of overfitting, we utilized a combined method of nested and repeated k-fold cross-validation. In the cross validation process, training sets were not used as test sets in each iteration. We consider that this method can mitigate the risk of overfitting compared with “leave-one-out cross validation. However, the data splitting method (training and validation) is not free from overfitting or model selection bias, and we need to validate our model with an external cohort. In order to validate our system, we just started new data collection, with several improvements including the use of another motion camera system with ease of portability that does not require calibration (OptiTrack V120: Trio, NaturalPoint Inc., USA). Using this system, we are now collecting Mocap data in cadaveric simulation trainings (laparoscopic nephrectomy task). Because it is a more complicated and long-duration task, we might be able to analyze the change of Mocap characteristics according to the progress of the task, with the hypothesis that experts have specific Mocap features in terms of “robustness” to long surgery. Furthermore, to clarify tacit knowledge regarding surgical dexterity, different approaches such as explainable artificial intelligence might be necessary. Nonetheless, the
machine learning algorithms automatically enabled us to assess surgical psychomotor skills based on the motion metrics of surgical instruments.

**Conclusions**

Using machine learning algorithms, we developed a Mocap-based skill assessment system in wet lab training, with a total GOALS score error of approximately 1–2 points, which can provide completely objective feedback to trainees. Our future challenges are the further improvement of onsite GOALS feedback, exploring the educational benefit of our model, and building an efficient training program.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00423-022-02505-9.

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**Declarations**

The institutional review board approved the present study (No. 018–0257).

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Conflict of interest** The authors declare no competing interests.

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