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順天堂醫事雜誌

June 2024

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(950th issue)

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JUNTENDO MEDICAL JOURNAL

順天堂醫事雑誌

The History of *Juntendo Medical Journal*

This *Juntendo Medical Journal* has been published under the Japanese name *Juntendo Igaku* (順天堂医学) from 1964 to 2012. However, the origin of *Juntendo Medical Journal* dates back to the oldest medical journal in Japan, *Juntendo Iji Zasshi* (順天堂醫事雑誌), which had been published between 1875 and 1877 (total of 8 issues). Between 1885 and 1886, Juntendo issued a limited release of a research journal titled *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) for a total of 39 issues.

In 1887, *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) was published with the government's approval and we used to regard this as the first issue of *Juntendo Medical Journal*. Since then, *Juntendo Medical Journal* has undergone a series of name changes: *Juntendo Iji Kenkyukai Zasshi* (順天堂醫事研究会雑誌), *Juntendo Igaku Zasshi* (順天堂医学雑誌), and *Juntendo Igaku* (順天堂医学).

Now in commemoration of the 175th anniversary of Juntendo University, starting with the first volume issued in 2013 (Volume 59 Number 1), we return to *Juntendo Medical Journal*'s original Japanese title in 1875-*Juntendo Iji Zasshi* (順天堂醫事雑誌). We also reconsidered the numbering of the journal and set the first issue in 1875 as the initial publication of *Juntendo Medical Journal*. The Volume-Number counting system and the English name *Juntendo Medical Journal* started in 1955 from the January 10 issue. Although this is not our intension, we will retain the Volume-Number counting system to avoid confusion. However, Volume 59 Number 1 will be the 882nd issue, reflecting the sum of all issues to date: 8 issues of *Juntendo Iji Zasshi* (順天堂醫事雑誌), 39 issues of *Houkoku* [*Juntendo Iji Kenkyukai*] (報告) (47 issues combined), and 834 issues from *Juntendo Iji Kenkyukai Houkoku* (順天堂醫事研究會報告) in 1887 to the present.

出典：小川秀興（OGAWA Hideoki, M.D., Ph.D.）：順天堂醫事雑誌（Juntendo Medical Journal）2013；59：6-10.

本誌は昭和39年（1964年）から平成24年（2012年）末まで『順天堂医学』として刊行されてきた．しかし，その起源は明治8年（1875年）から10年（1877年）にかけて発刊された日本最古の医学誌『順天堂醫事雑誌』（計8巻）にある．さらに明治18年（1885年）から19年（1886年）まで，会員限定配本として順天堂醫事研究會の雑誌『報告』（計39集）が発行されている．

その後『順天堂醫事研究會報告』が明治20年（1887年）に官許を受けて公刊されたので，順天堂ではこれを通刊1号としてきた．以来，『順天堂醫事研究会雑誌』，『順天堂医学雑誌』，『順天堂医学』と名称を変更して刊行されてきた．

今般，順天堂が創立175周年を迎える平成25年（2013年）の59巻1号を期して，本来の名称である『順天堂醫事雑誌』と復刻し，その起源である明治8年（1875年）第1巻をもって創刊号（通刊第1号）とすることとした．従来の巻号と欧文誌名は，昭和30年（1955年）1月10日発行のものを1巻1号としており，欧文誌名もこれより付け始めたもので不本意であるが，混乱を避けるためにこれらを継承する．ただし，通刊数は明治8年（1875年）から19年（1886年）にかけて刊行された『順天堂醫事雑誌』8巻分と順天堂醫事研究會の雑誌『報告』39集，計47巻分を通巻834号に加え，59巻1号を通刊882号とした．

出典：小川鼎三，酒井シヅ：順天堂医学　1980；26：414-418.
小川秀興：順天堂醫事雑誌　2013；59：6-10.

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Call for feature article proposals

To introduce the latest medical findings, Juntendo Medical Journal features a specific focus area for each issue. We would like to request all our readers to address any suggestions or proposals for suitable focus areas to our editorial office.

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From the illustrator: I bought a small banyan tree at a flower shop to use it as the subject of painting in my class. In Okinawa, they believe that a spirit, Kijimuna, dwells in this tree, and a banyan is an auspicious plant. After the lesson, I'm going to repot it in a larger container and grow it indoors.

Abstract

Juntendo Medical Journal
2024. 70(3), 192–194

Exploring the Dynamics of Oligodendrocyte Precursor Cell Differentiation in Three-dimensional Culture Systems

HINATA NISHIMURA

Research Institute for Diseases of Old Age, Juntendo University Graduate School of Medicine, Tokyo, Japan

Key words: chondroitin sulfate, extracellular matrix (ECM), oligodendrocytes, oligodendrocyte precursor cell (OPC), decellularized tissue

The goal of this study is to investigate the interactions between chondroitin sulfate (CS) chains and oligodendrocyte lineage cells (Figure 1a). Conventional two-dimensional (2D) culture systems do not adequately mimic the complex structure of the extracellular matrix (ECM) or simulate in vivo conditions. We previously developed a three-dimensional (3D) culture system based on a decellularized brain tissue1) and tested it using the oligodendrocyte cell line OL6[1)]. As the next step, the system was validated using primary cultures of oligodendroglial lineage. To evaluate neural stem cell differentiation in the 3D culture system, embryonic neurons were transplanted into the decellularized tissue; however, this approach was not successful because of the predominant differentiation of the neural stem cells into astrocytes. To enhance the differentiation of oligodendroglia, the standard protocol was optimized and cells were cultured in media supplemented with hepatocyte growth factor (HGF) and platelet-derived growth factor AA (PDGFAA). The schematic representation of this protocol is summarized in Figures 1b,c. One week after transplantation, the presence of oligodendrocyte precursor cells (OPCs), immature oligodendrocytes (iOL I), and mature oligodendrocytes was confirmed by immunostaining using differentiation-specific markers. A comparison between 2D and 3D cultures systems demonstrated that 3D conditions effectively induced the differentiation of neural stem cells into oligodendrocyte lineages (manuscript in preparation). The CS56 antibody staining results showed that the signal was stronger in 3D cultures compared to that in 2D cultures. These findings indicate that the 3D culture system provides optimal conditions for investigating the crosstalk between OPC differentiation and the ECM structure.

Acknowledgments

This work was performed at the Institute for Diseases of Old Age under Juntendo University Graduate School of Medicine. I am grateful to Juntendo Specialized Training for Aspiring Researchers for the generous support from the early stages of this work. I would like to thank Eri Arikawa-Hirasawa and Aurelien Kerever for their advice and help with the experimental design.

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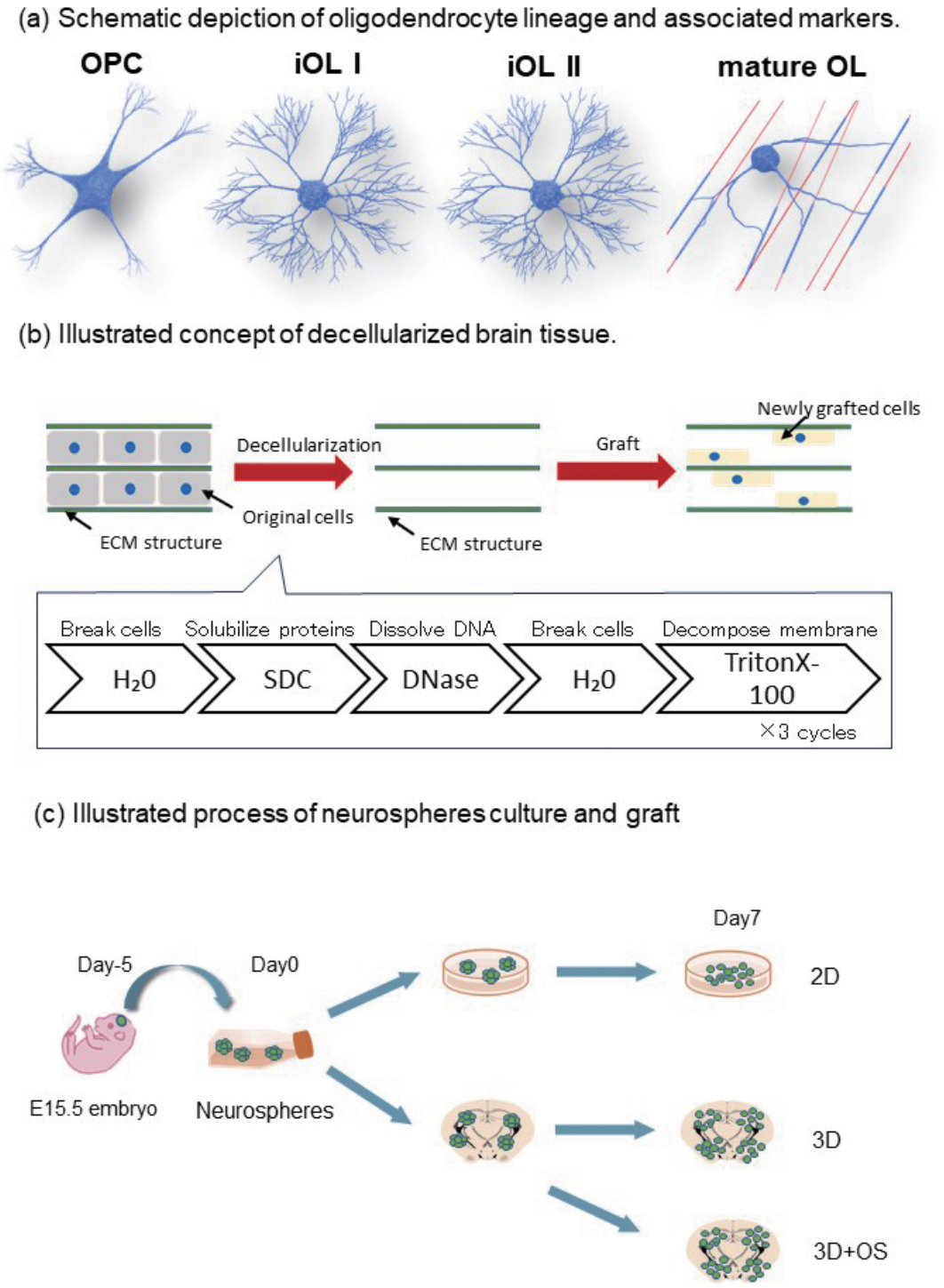

Figure 1 (a) Schematic representation of the oligodendrocyte lineage and its associated markers. (b) The diagram of decellularized brain tissue for grafting. Post-grafting, both 2D and 3D samples were cultured in a differentiation medium supplemented with hepatocyte growth factor (HGF). The "3D+OS" samples were cultured in an oligosphere medium containing both HGF and platelet-derived growth factor AA (PDGFAA).

Funding

No funding was received.

Author contributions

The author read and approved the final manuscript.

Conflicts of interest statement

The author declares that there are no conflicts of interest.

References

1) Kato K, Nishimura H, Suzuki Y, *et al*: Oligodendrocyte Cell Line OLP6 Successfully Differentiates on Decellularized Brain Tissue. Juntendo Med J, 2023; 69: 300–306.

Original Articles

Juntendo Medical Journal
2024. 70(3), 195–203

Development and Validation of a Machine Learning Model to Predict Post-dispatch Cancellation of Physician-staffed Rapid Car

TAKAAKI KAWASAKI, YOHEI HIRANO, YUTAKA KONDO, SHIGERU MATSUDA, KEN OKAMOTO

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Objectives: This study aimed to develop and validate a machine learning prediction model for post-dispatch cancellation of physician-staffed rapid car.

Materials: Data were extracted from the physician-staffed rapid response car database at our Hospital between April 2017 and March 2019.

Methods: After obtaining 2019 cases, we divided the dataset into a training set for developing the model and a test set for validation using stratified random sampling with an 8 : 2 allocation ratio. We selected random forest as the machine-learning classifier. The outcome was the post-dispatch cancellation of a rapid car. The model was trained using predictor variables, including 18 different reasons for rapid car request, age and gender of a patient, date (month), and distance from the hospital.

Results: This machine learning model predicted the occurrence of post-dispatch cancellation of rapid cars with an accuracy of 75.5% [95% confidence interval (CI): 71.0–79.6], sensitivity of 81.5% (CI: 75.0–86.9), specificity of 70.8% (CI: 64.4–76.6), and an area under the receiver operating characteristic value of 0.83 (CI: 0.79–0.87). The important features were distance from the hospital to the scene, age, suspicion of non-witnessed cardiac arrest, farthest geographic area, and date (months).

Conclusions: We developed a favorable machine learning model to predict post-dispatch cancellation of rapid cars in a local district. This study suggests the potential of machine-learning models in improving the efficiency of dispatching physicians outside hospitals.

Key words: machine learning, random forest, prediction, cancellation, rapid car

Introduction

The effectiveness of prehospital care provided by physicians remains controversial[1–4]. Some papers have demonstrated the clinical benefits of physician-staffed rapid car compared to regular ambulances, such as shortened time to intravenous thrombolytic therapy for patients with ischemic stroke or improved survival in out-of-hospital cardiac arrest[5,6]. However, implementing physician-staffed emergency services require human and financial resources. Therefore, appropriate selection of cases for physician mobilization should be made.

Juntendo University Urayasu Hospital has rapid car since 2013. A rapid car is a car that has a physician on board to provide pre-hospital medical care. And Our rapid cars covers about 60km^2. The crew members include one or two emergency physicians, one nurse, and two paramedics. The rapid car is operation from 9:00 am to 5:00 pm on weekdays and is dispatched about 700 cases in a year. They are requested by the fire department according to the criteria keywords included in the emergency request from the citizens. The criteria have 18

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items including CPA, endogenous diseases and exogenous diseases, and allows over-triage. After the dispatch, whether it was a cancelled or not, the reason for the dispatch, the time, and the location will be recorded.

The worst scenario for wasting medical resources is post-dispatch cancellation of physician-staffed emergency services. Post-dispatch cancellation of services is common due to the incomplete information provided by citizens and the delay in physician-staffed emergency services reaching the site. Although there are no clear criteria, ambulance crew might cancel a rapid car request when the ambulance have already arrived at the scene and was ready to transport to the hospital. They also might cancel it when they think that a patient does not need any care by a physician at the site. A rapid car crew sometimes cancel the request because they were working for another case. As cancelation of a rapid car does not involve any out-of-hospital activities by the physician and only results in wastage of human and financial resources, a strategy to reduce the number of post-dispatch cancellation is needed.

Few reports[7–10] have identified the factors responsible for post-dispatch cancellation. Understanding these factors is crucial as it would contribute to optimization of the dispatch criteria for prehospital emergency services. However, predicting the occurrence of cancellation before a physician-staffed vehicle is dispatched from the hospital would be more valuable.

The accuracy and effectiveness of prediction models using machine learning have been described in the recent years[11, 12]. In addition to their high predictive performance, machine-learning models can return prediction results for each case. Thus, developing a prediction model based on machine learning may be a solution to minimize the number of post-dispatch cancellations.

Therefore, we aimed to develop and validate a machine-learning model to predict post-dispatch cancellation of physician-staffed rapid cars.

Materials and Methods

Data sources and Ethical considerations

The data for this study was obtained from the physician-staffed rapid response car (RRC) database at Juntendo University Urayasu Hospital between April 2017 and August 2020 The database included all rapid car cases dispatched from the hospital. This RRC system covered a total population of 660,435 and total area of 74.69 km^2 in the districts of Urayasu and Ichikawa city in the Chiba prefecture of Japan. The following information were retrieved from the database: date; age, and sex of the patient; reason for RRC request; location of the scene; occurrence of cancellation; reason for cancellation; and the hospital to which the patient was transported. The details of the database and rapid car system at our institute have been described previously[10].

The study protocol was approved by the Ethics Committee of the Juntendo University Urayasu Hospital (E22-0450). The requirement for informed consent was waived owing to the retrospective observational design of the study. All the procedures conducted in this study were in accordance with the tenets of Declaration of Helsinki.

Study population

The study population comprised all the patients to whom RRC was dispatched from the hospital. A flow diagram of patient inclusion is shown in Figure 1. During the study period, 2299 requests were made for physician-staffed rapid car dispatch. However, 82 cases were excluded from analysis as the cars were not dispatched due to various reasons. Subsequently, we excluded 47 cases that did not meet the dispatch criteria and 151 cases with insufficient information. Thus, 2019 cases were included in this study. Finally, the dataset was divided into training (n=1615) and test sets (n=404) by stratified random sampling with an 8:2 allocation ratio.

Predictor variables and outcome

Data regarding five variables, including date, age, sex, location of the scene, and reasons of requests, were retrieved from the database. We used these parameters as outcome predictors. Only the information of the month was used in the 'date' variable. To train the machine learning model, information on location of the scene was changed to distance between the hospital and the scene. In addition, the three kinds of categorical area (area 1: the nearest, area 3: the farthest district from the hospital) on the basis of the medical control region were delineated. The 'reasons of request' variable

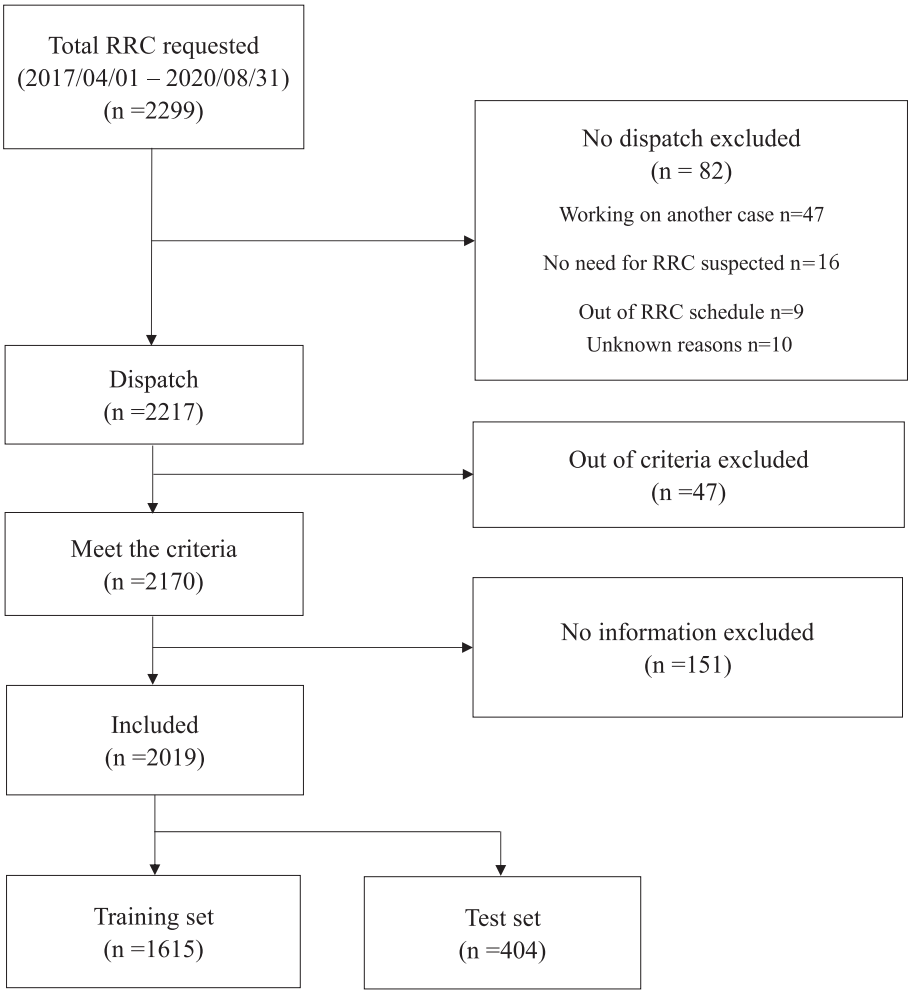


Figure 1 Flow diagram of this study
RRC: rapid response car.

comprised 18 different reasons: suspicion of unwitnessed cardiac arrest, suspicion of witnessed cardiac arrest, chest pain and/or back pain, neurological deficit and/or severe headache, unconsciousness, convulsion, dyspnea, suspected hemorrhagic shock, traffic injury, fall, crush injury, penetrating injury, burn, drowning, airway obstruction, hanging, poisoning, and anaphylaxis. The outcome was the post-dispatch cancellation of a rapid car.

Development and validation of a machine learning model

We trained and developed a random forest machine learning model using the training data for outcome prediction. During the development process, we performed 10-fold stratified cross-validation to avoid overfitting the model. In addition, the hyperparameters were optimized to obtain the best performance for outcome prediction. Internal validation of the developed model was performed using the test data. We computed the area under the receiver operating characteristic (AUROC) curve, sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, negative predictive value, and accuracy of the developed model for validation. In addition, important features for developing the model were assessed by calculating the normalized total reduction of the criterion brought about by the feature known as Gini importance[13].

Furthermore, machine learning prediction models for clinical use should be tuned according to the purpose of the model. Therefore, we compared the confusion matrices and statistical measures among six kinds of machine learning models with different binary classification thresholds ranging between 0.3 and 0.7 at intervals of 0.1.

Statistical analysis and software library

Continuous variables, such as age and distance from the hospital, were reported as medians and interquartile range. Categorical variables were presented as raw counts and percentages. The Mann–Whitney U test was used to compare the median of the two samples. Chi-square test was used to compare frequencies. Two-sided significance level for all tests was set at 5% ($p < 0.05$). Analyses of the characteristics of the included cases were performed using EZR software version 3.3.2 (EasyR, Saitama Medical Center, Jichi Medical University, Saitama, Japan)[14]. ScikitG-learn (version 0.21.3) with Python (version 3.7.4, in Anaconda 2019.10) was used for model development.

Results

Characteristics of study participants

The characteristics of the cohorts used for machine learning development and internal validation are presented in Table 1. The number of post-dispatch cancellations in 2019 cases were 891 (44.1%). Of these, males accounted for 58.7%, and the median age was 71 years old. The median distance from the hospital to the location of the scene was 7.8km. The most common reason for rapid car requests was unwitnessed, suspected cardiac arrest [522 cases, (25.9%)] followed by dyspnea [346 cases, (17.1%)]. Comparison between the training and test data showed no statistical difference in any of the variables used for the development of the machine learning algorithm, suggesting that they were evenly distributed.

Performance of the developed machine learning model

The receiver operating characteristic (ROC) curve, confusion matrix, and statistical measures evaluated to validate the performance of the developed machine learning model in the test set are shown in Figure 2. The ROC curve and its AUROC value demonstrated good ability of the model to predict post-dispatch cancellation (AUROC: 0.83 [95% confidence interval (CI): 0.79–0.87]). The model predicted the outcome correctly with an accuracy of 75.5% (CI: 71.0– 79.6). The sensitivity, specificity, positive predictive value, and negative predictive value were 81.5% (CI: 75.0–86.9), 70.8% (CI: 64.4–76.6), 68.7% (CI: 63.9–73.1), and 82.9% (CI: 77.9–87.0), respectively.

Variable importance for model development

Figure 3 shows the Gini importance of the variables used in the development of the model. Distance from the hospital was the most important feature in predicting the occurrence of post-dispatch cancellation, followed by patient's age, unwitnessed/suspected cardiac arrest, farthest region from the medical control area (area 3), and the month of dispatch for the rapid car. These factors were among the top five important features.

Comparison of statistical measures among machine learning models with different classification thresholds in validation

The statistical measures of the machine learning models with different binary classification thresholds are shown in Table 2. Under the threshold of 0.3, the developed model showed a sensitivity of 89.9% (CI: 84.5–93.9), specificity of 58.4% (CI: 51.7–64.9), positive predictive value of 63.0% (CI: 59.1–66.7), and negative predictive value of 88% (CI: 82.4–92.0). In contrast, the developed model under the threshold of 0.8 demonstrated a sensitivity of 38.2% (CI: 31.0–45.8), specificity of 91.2% (CI: 86.7–94.5), positive predictive value of 77.3% (CI: 68.3–84.3), and negative predictive value of 65.2% (CI: 62.3–67.9).

Discussion

To the best of our knowledge, this study is the first to develop and validate a machine learning model to predict the occurrence of post-dispatch cancellation of physician-staffed emergency service. Using a single-center database, we developed a random forest-based prediction model that showed favorable performance in predicting post-dispatch cancellation in the internal validation with a reasonably high AUROC of 0.83.

Several studies have demonstrated the effect of prehospital care[15, 16]. However, only a few studies have focused on human or financial cost-effectiveness of prehospital care[7–9]. Although there have been few reports on cost-effectiveness of prehospital care using helicopters, physician-staffed RRC has received little attention.

It is important that overtriage of RRC cancellations should be tolerated because it is hard to select

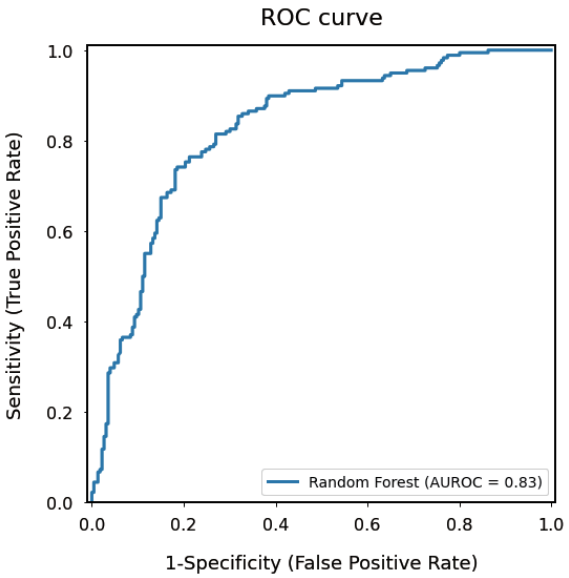
Table 1 Characteristics of the datasets

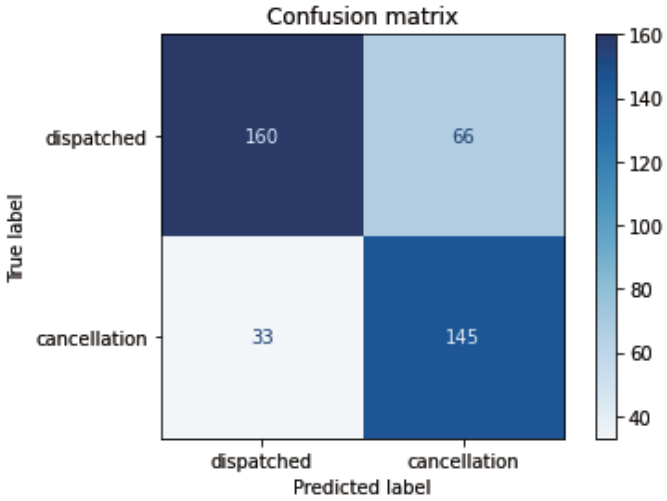
Variable	All (n=2019)	Training data (n=1615)	Test data (n=404)	P value
Age (years)	71 [31]	71 [31]	72 [30]	0.61
Gender (male)	1185 (58.7%)	952 (58.9%)	233 (57.7%)	0.64
Distance from the hospital (km)	7.8 [9.5]	7.8 [9.5]	8.9 [10.7]	0.48
EMS regional area				0.44
Area 1	527 (26.1%)	419 (25.9%)	108 (26.7%)	
Area 2	478 (23.7%)	392 (24.3%)	86 (21.3%)	
Area 3	1014 (50.2%)	804 (49.8%)	210 (52.0%)	
Month				
March–May	434(21.5%)	336(20.8%)	98(24.2%)	0.10
June–August	579(28.6%)	473(29.2%)	106(26.2%)	
September–November	472(23.3%)	388(24.0%)	84(20.7%)	
December–February	534(26.4%)	418(25.8%)	116(28.7%)	
Reason of RRC request				0.59
Suspected cardiac arrest (unwitnessed)	522 (25.9%)	407 (25.2%)	115 (28.5%)	
Suspected cardiac arrest (witnessed)	63 (3.1%)	51 (3.2%)	12 (3.0%)	
Chest pain and/or back pain	180 (8.9%)	138 (8.5%)	42 (10.4%)	
Neurological deficit and/or severe headache	219 (10.8%)	182 (11.3%)	37 (9.2%)	
Unconsciousness	231 (11.4%)	183 (11.3%)	48 (11.9%)	
Convulsion	77 (3.8%)	64 (4.0%)	13 (3.2%)	
Dyspnea	346 (17.1%)	286 (17.7%)	60 (14.9%)	
Suspected hemorrhagic shock	29 (1.4%)	24 (1.5%)	5 (1.2%)	
Traffic injury	70 (3.5%)	54 (3.3%)	16 (4.0%)	
Fall	82 (4.1%)	68 (4.2%)	14 (3.5%)	
Crush injury	14 (0.7%)	8 (0.5%)	6 (1.5%)	
Penetrating injury	4 (0.2%)	3 (0.2%)	1 (0.2%)	
Burn	6 (0.3%)	5 (0.3%)	1 (0.2%)	
Drowing	12 (0.6%)	10 (0.6%)	2 (0.5%)	
Airway obstruction	39 (1.9%)	31 (1.9%)	8 (2.0%)	
Hanging	37 (1.8%)	34 (2.1%)	3 (0.7%)	
Poisoning	8 (0.4%)	6 (0.4%)	2 (0.5%)	
Anaphylaxis	56 (2.8%)	42 (2.6%)	14 (3.5%)	
Outcome				
Cancellation	891 (44.1%)	713 (44.1%)	178 (44.1%)	0.97

All categorical variables are shown as n (%). A continuous variables are shown as median [interquartile range]. EMS: Emergency Medical Service. RRC:Rapid Response Car

the exact patients who receive benefits by a rapid intervention of a physician at the site. However, we suggest that post-dispatch cancellation should be debated more seriously as it meant that nurses and physicians acted ineffectively outside the hospital. Rapid car stuff including physicians and nurses not only care the patients in the prehospital settings, but they also care other patients in the hospital. We believe that their presence in hospitals may have elevated the efficiency of in-hospital patient care of other sick patients. In such scenario, it is important to optimize the distribution of valuable human resources.

As the rapid car system at our institute has a very low dispatch threshold, it has a very high post-dispatch cancellation rate (44.1%). Thus, the





Statistical measures	Value	95% CI
Sensitivity	81.5%	75.0 – 86.9
Specificity	70.8%	64.4 – 76.6
Positive Predictive Value	68.7%	63.9 – 73.1
Negative Predictive Value	82.9%	77.9 – 87.0
Accuracy	75.5%	71.0 – 79.6
AUROC	0.83	0.79 - 0.87

Figure 2 Performance of the developed machine learning model for outcome prediction in validation
AUROC: the area under the receiver operating characteristic, CI: confidence interval.

database with balanced outcomes used in this study was valuable for assessing the optimization of post-dispatch cancellation rate by creating and validating machine learning models. Our machine learning model showed favorable predictive performance for post-dispatch cancellation, with an AUROC of 0.83. Thus, we might have a chance to optimize the rate of post-dispatch cancellation. In other words, we could decide not to dispatch to the site in some cases by using the predictive model when the RRC was requested. It is sure that the final decision in the medical situation should be done by medical professionals, however; the data-driven prediction such as machine learning would support us make important decisions[17–19]. The prediction model is especially useful for medical professionals when human prediction is difficult.

Nevertheless, maintaining a fine balance between therapeutic effectiveness and resource consumption remains challenging. Reduction in the cancellation rate using the prediction model would be accompanied by an increased number of cases of no RRC dispatch wherein RRC involvement would have resulted in beneficial effects on patient outcome. The acceptable cancellation rate for RRC should change depending on the circumstance of the region or sufficiency of human resources of the facility. From this perspective, we developed a variety of machine learning prediction models by altering the binary threshold of positivity of prediction. As shown in Table 2, alteration of the binary thresholds provided a choice of prediction models with a variety of sensitivity and specificity. In contrast to the existing and conventional prediction tools, machine learning models can be tuned specifically. Therefore, medical facilities can select the best model to fit their purpose and achieve their acceptable level of RRC cancellation rate.

The most critical feature for the development of our machine learning model was the distance between the patient location and the hospital. If the distance from the scene to the hospital where

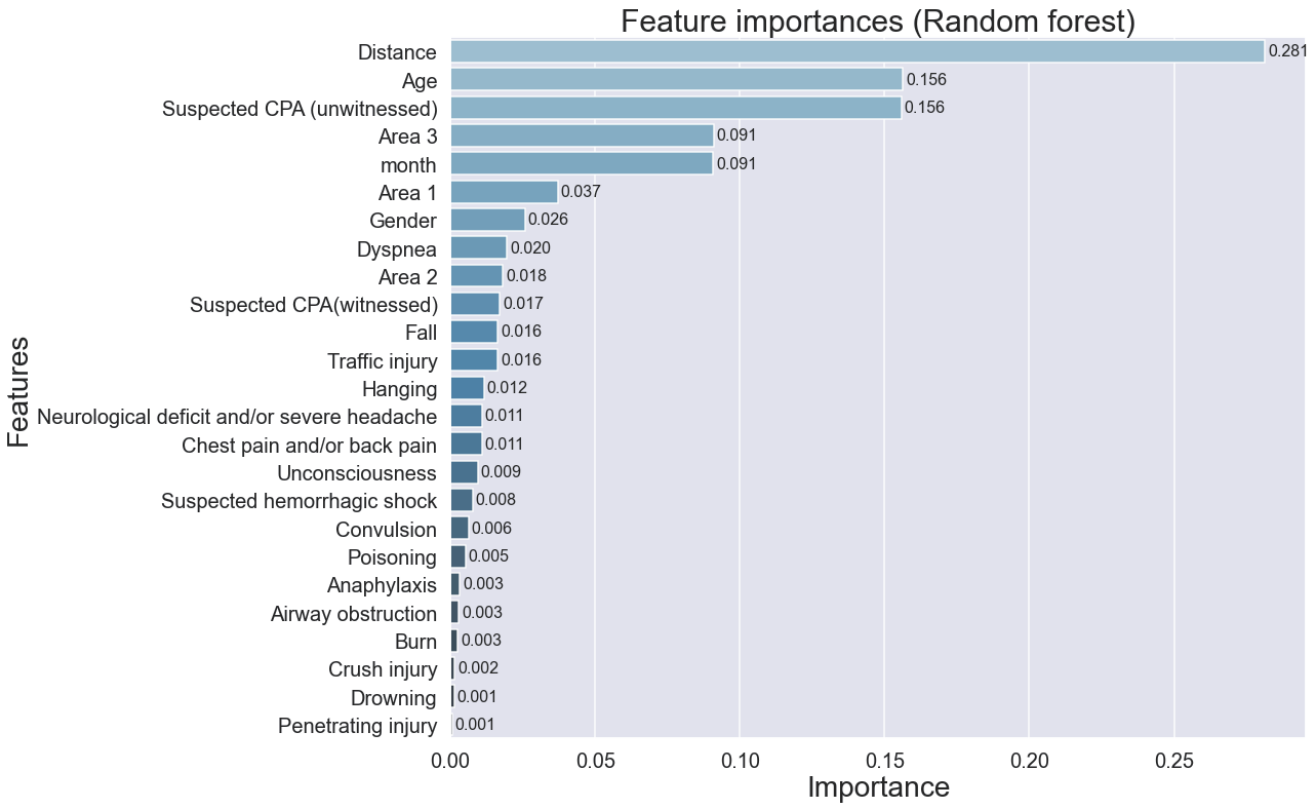


Figure 3 Feature importance to develop the machine learning model
CPA: cardio-pulmonary arrest

Table 2 Comparison of statistical measures among machine learning models with different classification thresholds in validation

Statistical measures	Threshold					
	0.3	0.4	0.5	0.6	0.7	0.8
Sensitivity	89.9(%)	86.0(%)	81.5(%)	76.4(%)	59.6(%)	38.2(%)
Specificity	58.4(%)	66.3(%)	70.8(%)	77.4(%)	85.8(%)	91.2(%)
Positive predictive value	63.0(%)	66.8(%)	68.7(%)	72.7(%)	76.8(%)	77.3(%)
Negative predictive value	88.0(%)	85.7(%)	82.9(%)	80.7(%)	72.9(%)	65.2(%)
Accuracy	72.3(%)	75.0(%)	75.5(%)	77.0(%)	74.2(%)	67.8(%)

AUROC: the area under the receiver operating characteristic, CI: confidence interval.

the RRC is dispatched is long, it is more likely that the first arriving emergency medical service (ambulance crew) will decide where to transport the patient before the RRC arrives, hence the cancellation rate of the RRC might increases.

Interestingly, patient age and month of request for RRC were also key predictors in developing the model. As whether to accept patient transport to the hospital is usually dependent on the decision of each hospital's physician in Japan, it is possible that patient age or seasonal increase in patient transport may have affected the acceptance rate of hospital transport and thus, led to the alteration of cancellation rate of RRC. For example, elderly patients with a variety of comorbidity or shortage of hospital beds in winter might be strong negative factors for the determination of the hospital where the patient will be transported. In this case, the need for RRC may increase and the cancellation rate would decrease.

Assessment of the feature importance of the model also provides us information to modify the conventional request criteria for RRC from the fire department. In our cases, alteration of the covering area of the RRC or removing unwitnessed/suspected cardiac arrest from the reason of RRC request is the candidate for new rule for RRC dispatch to decrease the cancelation rate, although we should

consider the negative clinical effects due to these changes.

This study had a few limitations. First, our machine learning model was developed using a single-center database. Therefore, the results cannot be generalized to other institutions or regions. Development and validation of a machine learning model using datasets derived from each facility is anticipated. Second, very few important features, such as crush injury, drowning, and penetrating injuries, were used to develop the model. However, it is important to exercise caution when interpreting the impact of these parameters on post-dispatch cancellation owing to the limited sample size of the data. Third, sometimes it is difficult to obtain all the necessary information for designing a prediction model. As it is required that an early decision should be made for dispatching RRC, we should not stick to obtaining sufficient prehospital information to use the prediction model. Finally, the machine learning model requires the input of variables in the application when used in clinical settings. Thus, its usability for physicians might be inferior to the conventional RRC dispatch criteria. However, this disadvantage can be overcome by using technologies such as speech recognition.

In conclusion, we developed a favorable machine learning model to predict post-dispatch cancellation of rapid cars in a local district. Although each medical institution would have to adjust the model according to the region or facility, the current study demonstrated the potential of the machine learning-based prediction model to optimize post-dispatch cancellation of physician-staffed rapid cars.

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Author contributions

TK and YH analyzed and interpreted the patient data regarding post-dispatch cancellation of physician-staffed rapid response car. All authors have read and approved the final manuscript.

Conflicts of interest statement

YH is the Chief Executive Officer, MedPop Co. Ltd. None of the other authors declare no conflict of interest.

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Original Articles

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Impact of the Aboral Pouch in Roux-en-Y Reconstruction after Laparoscopic Total Gastrectomy for Elderly Patients

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Objectives: The number of elderly people with stomach cancer is increasing; therefore, minimally invasive surgical treatments are required. Elderly patients have multiple comorbidities and are prone to postoperative weight loss, nutritional disorders, Postgastrectomy syndrome (PGS), and decreased quality of life (QOL). Total gastrectomy is particularly associated with these complications, although aboral-pouch creation reportedly improves the condition by compensating for lost reservoir capacity. However, there is no consensus regarding its significance. This study aimed to investigate the impact of the aboral pouch on total gastrectomy outcomes in elderly patients.

Materials and Methods: Thirty-six patients who met the eligibility criteria, defined as elderly patients aged ≥75 years, were retrospectively analyzed. The patients had undergone Roux-en-Y reconstructions with an aboral pouch in laparoscopic total gastrectomy procedures performed at Juntendo University from July 2016 to June 2022. The main outcomes were postoperative nutritional status, PGS, and QOL.

Results: The average postoperative period was approximately 1 year (12.0 *vs.* 13.5 months, P=0.536), for 14 elderly and 22 non-elderly patients, respectively. Elderly patients had more comorbidities (78.5% *vs.* 40.9%, P=0.041). The outcome of nutritional status demonstrated no differences in weight-loss rate (−5.3% *vs.* −8.6%, P=0.651) or prognostic nutritional status (−7.9% *vs.* −5.9%, P=0.243). There was no significant difference in PGS and QOL between elderly and non-elderly patients.

Conclusions: Total gastrectomy with an aboral-pouch creation could be beneficial for elderly 43 patients from the perspective of postoperative nutritional status, PGS, and QOL.

Key words: aboral pouches, aged, postgastrectomy syndromes, gastrectomy

Introduction

Total gastrectomy is the gold standard of treatment for upper-stomach cancers. Recently, with the aging of society, the number of elderly individuals requiring surgical treatment for gastric cancer has increased. Many elderly patients who require treatment have multiple comorbidities and are at a higher risk of postoperative complications than their non-elderly counterparts[1–3)]. Furthermore, elderly patients who have undergone gastrectomy procedures have a high weight-loss rate and are more prone to developing severe postoperative nutritional problems[4)]. Postgastrectomy syndrome (PGS), which is specific to gastric surgery, occurs frequently after gastrectomy and requires attention as a clinical condition, because it is closely related to weight loss and nutritional disorders and adversely affects

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quality of life (QOL)[5-7]. Specifically, compared with other gastrectomy procedures, total gastrectomy, wherein removal of the entire stomach significantly reduces reservoir capacity, is associated with more frequent weight loss, nutritional disorders, and decreased QOL due to PGS[6,7].

Weight loss after total gastrectomy occurs in approximately 10–15% of cases. Decreased food intake and esophageal reflux symptoms due to bile reflux are particularly well-known causes[5-8]. Several reconstructive innovations reportedly improve PGS and QOL postoperatively in patients who have undergone total gastrectomy procedures. However, the best practice has not yet been established[8,9].

One method known to improve the reservoir capacity function after total gastrectomy is the addition of a jejunal pouch to the reconstruction. This pouch, created in the Y limb of Roux-en-Y reconstruction, is called the aboral pouch[8,10,11]. Despite several reports on the usefulness of aboral pouches, there is no consensus regarding the safety and benefits of aboral pouches in elderly patients. Herein, we aimed to examine the effect of aboral-pouch creation after laparoscopic total gastrectomy in elderly patients in terms of outcomes such as nutritional status, PGS, and QOL.

Materials and Methods

Patients and data collection

From July 2016 to June 2020, 60 consecutive gastric cancer patients underwent laparoscopic total gastrectomy at Juntendo University Hospital. Of these, 36 patients in whom R0 resection was obtained, no recurrence occurred, and the Postgastrectomy Syndrome Assessment Scale-37 (PGSAS-37) questionnaire was completed and recorded were included. Herein, elderly patients were defined as those aged ≥75 years. For comparison during analysis, the patients were grouped into those aged ≥75 years (elderly) and <75 years (non-elderly) (Figure 1). Clinical, pathological, perioperative, nutritional status, and the PGSAS-37 questionnaire data were retrospectively evaluated. Clinicopathological data included the postoperative period, sex, body mass index (BMI), comorbidities, lymph-node dissection extent, pathological stage, and combined resection. Perioperative outcomes included surgical approach, conversion to open surgery, operative time, blood-loss volume, postoperative complications, hospital-stay length, and adjuvant chemotherapy. The pathological diagnosis was determined with reference to the Japanese gastric cancer classification[12]. Postoperative complications were classified using the Clavien-Dindo classification system[13]. Nutritional status was evaluated based on body weight, total protein, albumin, lymphocyte count, and prognostic nutritional index (PNI)[14]. The rate of change between 1 year postoperatively and preoperatively was determined.

This study was conducted in accordance with

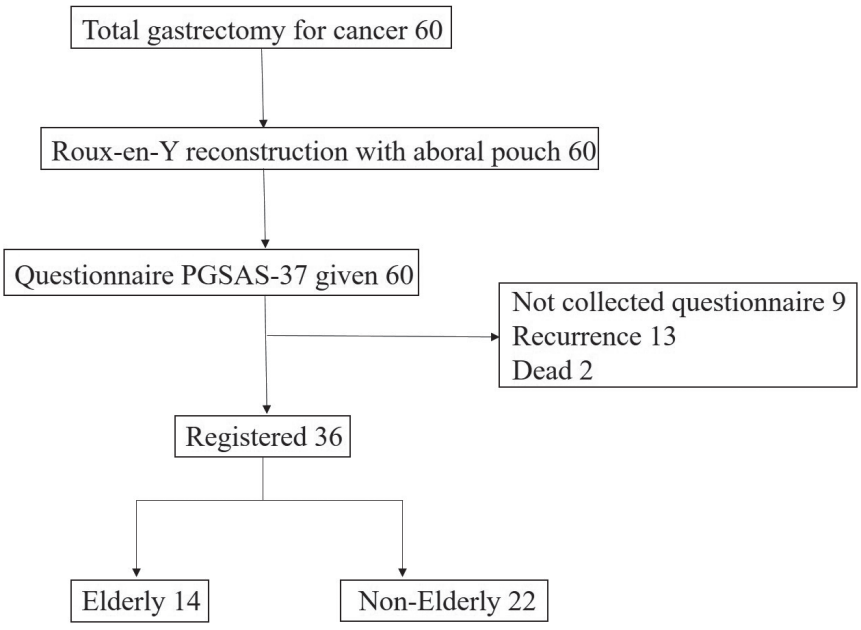

Figure 1 Flow diagram of this study

the principles of the Declaration of Helsinki. The study protocol was approved by the Juntendo University Hospital Ethics Review Board according to our clinical ethics regulations (approval no. E22-0412). The requirement for informed consent was waived owing to the retrospective and observational nature of the study. An opt-out approach was used by providing access to written disclosure on the study website (URL: https://www.gcprec.juntendo.ac.jp/kenkyu/detail/5380).

PGSAS-37

We used the PGSAS-37, established as the national average database in Japan by the Japanese Postgastrectomy Syndrome Working Party (JPGSWP), to compare PGS and QOL in elderly patients with those in non-elderly patients[15, 16]. The PGSAS-37 is a disease-specific scale used to assess the subjective symptoms and living conditions in patients who have undergone gastrectomy procedures[15]. PGSAS-37 comprises various QOL questionnaires on the Gastrointestinal Symptom Rating Scale (GSRS)[17] and includes 37 items, 15 derived from the GSRS and 22 originally selected as clinically relevant by the JPGSWP. These additional 22 items include 8, 2, 5, 3, and 3 items to assess global symptoms, dumping syndrome, food quantity, food quality, and work status, respectively. Furthermore, it includes one item and three items that rate dissatisfaction with life. These 37 items were aggregated into 9 subscales for 17 primary endpoints. The nine subscales were calculated from the mean values of applicable items. The main outcomes include symptoms, living status, and QOL (Figure 2). High scores for the following items indicated good QOL: food intake, appetite, hunger, satiety, food quality, and bodyweight changes. Low scores for other items indicated a good QOL. The questionnaire was administered to patients at the time of the outpatient visit by a doctor or nurse and was completed in the waiting room by the patient under stress-free conditions. A medical clerk managed data acquisition.

Aboral pouch

Two types of jejunal pouches are used for Roux-en-Y reconstruction after total gastrectomy. One method involves the creation of a jejunal pouch in the Roux limb of the esophagojejunostomy and the other involves the creation of a jejunal pouch in the Y limb, known as the aboral pouch. Both methods often use a linear stapler to add to the reconstruction. There is no fixed definition of pouch size or method for creating the pouch; however, in practice, a more convenient aboral pouch is likely to be preferred[8, 11, 18].

The following method was routinely practiced to create aboral pouches: after lymph node dissection and gastrectomy, a small incision was made in the umbilicus. The jejunum was lifted, and an aboral pouch was added to the Y limb, which was created as a side-to-side anastomosis 45 cm distal to the esophagojejunostomy. This procedure for creating a Y-limb with an aboral pouch involved shaping by firing a 60-mm linear stapler from the entry hole of the jejunum to each of the proximal and distal sides. The stapler insertion hole was closed with a handsaw Gambee suture using a braided absorbable suture. Created using two 60-mm linear staplers, the pouch shrinks to approximately 90 mm in length (Figure 3).

Statistical analysis

We used independent t-tests to compare continuous variables and Fisher's exact test to compare categorical variables. Statistical significance was defined as a two-tailed P-value of <0.05. All statistical analyses were performed using StatMate statistical software (version V; GraphPad Software, San Diego, CA, USA). The PGSAS statistical kit was used to compare PGS and QOL between the elderly and non-elderly groups.

Results

Clinicopathological characteristics

Table 1 demonstrates the clinicopathological characteristics of the elderly (≥ 75 years) and non-elderly (< 75 years) groups. There were 14 patients in the elderly group and 22 in the non-elderly group. Patients in the elderly group had significantly more comorbidities than those in the non-elderly group (78.5% *vs.* 40.9%; $P=0.041$). There was no significant difference in the postoperative period recorded in months, sex, preoperative BMI, extent of lymph node dissection, pStage, and combined resection between the two groups.

Symptom item		Subscales
1	Abdominal pains	Esophageal reflux subscale (items 2, 3, 5, 16)
2	Heartburn	Abdominal pain subscale (items 1, 4, 20)
3	Acid regurgitation	Meal-related distress subscale (items 17-19)
4	Sucking sensations in the epigastrium	Indigestion subscale (items 6-9)
5	Nausea and vomiting	Diarrhea subscale (items 11, 12, 14)
6	Borborygmus	Constipation subscale (items 10, 13, 15)
7	Abdominal distension	Dumping subscale (items 22, 23, 25)
8	Eructation	
9	Increased flatus	Total symptom score (above than seven subscale)
10	Decreased passage of stools	
11	Increased passage of stools	
12	Loose stools	
13	Hard stools	
14	Urgent need for defecation	
15	Feeling of incomplete evacuation	
16	Bile regurgitation	
17	Sense of foods sticking	
18	Postprandial fullness	
19	Early satiation	
20	Lower abdominal pains	
21	Number and type of early dumping symptoms	
22	Early dumping, general symptoms	
23	Early dumping, abdominal symptoms	
24	Number and type of late dumping symptoms	
25	Late dumping symptoms	
Living status item		
26	Ingested amount of food per meal	
27	Ingested amount of food per day	
28	Frequency of main meals	
29	Frequency of additional meals	
30	Appetite	Quality of ingestion subscale (items 30-32)
31	Hunger feeling	
32	Satiety feeling	
33	Necessity for additional meals	
34	Ability for working	
Quality of life item		
35	Dissatisfaction with symptoms	Dissatisfaction with daily life subscale (items 35-37)
36	Dissatisfaction at the meal	
37	Dissatisfaction with working	

Figure 2 Structure of Postgastrectomy Syndrome Assessment Scale-37

Perioperative outcome

The perioperative outcomes are summarized in Table 2. All patients underwent laparoscopic surgery; for one elderly patient, the procedure was converted to open surgery. There were no significant differences in operative time or intraoperative blood loss. Postoperative complications of Clavien-Dindo grade ≥3 were observed in two (14.3%) and three (13.6 %) patients in the elderly and non-elderly groups, respectively. There were no anastomotic-related

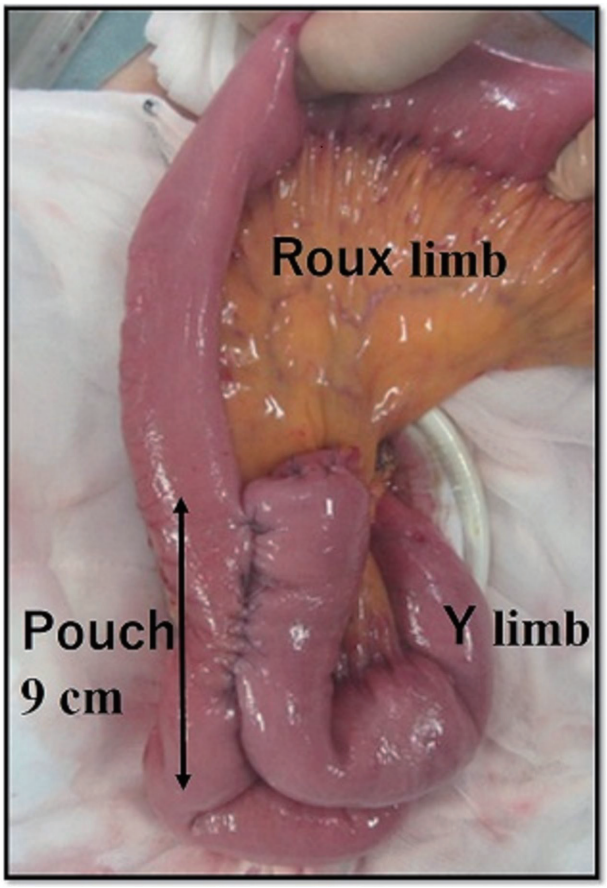

Figure 3 Aboral pouch

complications including the aboral pouch in both groups. The postoperative hospital stay was 17.0 and 13.2 days in the elderly and non-elderly groups, respectively (P=0.333).

Nutritional Status

The nutritional status is summarized in Table 3. There was no significant difference in weight loss between the elderly and non-elderly groups (-5.3% *vs*. -8.6%, P=0.651). There was no significant difference in total protein, albumin, total lymphocyte count, or PNI (-7.9% in the elderly group *vs*. -5.9% in the non-elderly group, P=0.243) between the two groups.

PGS and QOL

No significant differences in symptom categories were observed between the elderly and non-elderly groups (Table 4). Furthermore, no significant differences in living status or QOL were observed between the two groups (Table 5).

Discussion

This is the first report to evaluate the aboral-pouch addition to Roux-en-Y reconstruction after laparoscopic total gastrectomy procedure in elderly patients. This study is significant because it evaluated aboral-pouch addition from multiple perspectives, including perioperative outcomes, postoperative nutritional status, PGS, and QOL, and demonstrated its safety and feasibility in elderly patients with gastric cancer for whom total gastrectomy is indicated.

The core treatment for gastric cancer is surgical resection. Total gastrectomy is required for cura-

Table 1 Patient clinicopathological characteristics

Variable	Elderly group (n=14)	Non-elderly group (n=22)	Univariable P-value
Age, years, mean (±SD)	79.3 (±4.25)	62.8 (±10.7)	<0.001
Postoperative period in months (±SD)	12.0 (±8.94)	13.5 (±7.96)	0.536
Male, n (%)	8 (57.1)	14 (63.6)	0.738
Preoperative BMI in kg/m^2 (±SD)	21.1 (±3.3)	22.4 (±4.5)	0.388
Comorbidity, n (%)	11 (78.5)	9 (40.9)	0.041
Extent of lymph node dissection, n			0.441
D1+	2	6	
D2	12	16	
pStage, n			0.255
I	4	11	
II	3	6	
III	7	5	
Combined resection, n (%)	4 (28.5)	3 (13.6)	0.349

BMI, body mass index; SD, standard deviation

Table 2 Perioperative outcomes

Variable	Elderly group (n=14)	Non-elderly group (n=22)	Univariable *P*-value
Approach, n			1.000
Robotic	1	1	
Laparoscopic	13	21	
Conversion to open surgery, n (%)	1 (7.1)	0	0.389
Operative time, min (±SD)	345 (±114)	359 (±98)	0.172
Blood loss, mL (±SD)	104 (±148)	56.0 (±55.9)	0.705
Postoperative complication CD ≥3, n (%)	2 (14.3)	3 (13.6)	1.000
Pneumoniae, n	1	0	
Surgical site infection, n	1	3	
Anastomotic-related complication including the aboral pouch	0	0	
Postoperative hospital stay in days (±SD)	17 (±71.1)	13 (±19.7)	0.333

CD, Clavien-Dindo; SD, standard deviation

Table 3 Nutritional status

Variable	Elderly group (n=14)	Non-elderly group (n=22)	Univariable *P*-value
Body weight % (±SD)	−5.3 % (±20.0)	−8.6 % (±23.8)	0.666
Total protein % (±SD)	3.7 % (±30.1)	−0.2 % (±10.3)	0.585
Albumin % (±SD)	−7.4 % (±43.0)	3.2 % (±44.5)	0.389
Total lymphocyte count % (±SD)	−7.5 % (±42.1)	1.3 % (±31.7)	0.476
PNI % (±SD)	−7.9 % (±38.2)	−5.9 % (±31.4)	0.243

PNI, prognostic nutritional index; SD, standard deviation
Nutritional Status (%): (1 year postoperatively-preoperatively)/preoperatively × 100

Table 4 PGSAS score for symptom categories

		Elderly group n=14		Non-elderly group n=24		*P*-value
		mean	SD	mean	SD	
Symptom	Esophageal reflux subscale	1.9	0.8	2.5	1.0	0.074
	Abdominal pain subscale	2.5	1.2	3.2	1.2	0.091
	Meal-related distress subscale	1.5	0.9	1.7	0.8	0.469
	Indigestion subscale	2.1	0.9	2.3	0.6	0.464
	Diarrhea subscale	2.2	1.9	1.9	1.3	0.604
	Constipation subscale	2.4	1.2	1.9	1.9	0.327
	Dumping subscale	1.7	1.0	1.9	1.9	0.674
	Total symptoms score	2.1	0.7	2.1	0.5	1.000

PGSAS, Postgastrectomy Syndrome Assessment Scale

tive resection of cancers occupying the upper part of the stomach. Roux-en-Y is the most common type of reconstruction performed after total gastrectomy globally[19]. However, reservoir capacity reduction due to total gastrectomy is the main cause of poor nutritional status, PGS, and QOL post-procedure[1]. Recently, the number of elderly patients requiring total gastrectomy has been increasing due to the aging population. These elderly patients are at high risk for postoperative complications, nutritional disorders, PGS, and reduced QOL post-operatively[2-4]. Therefore, we focused on aboral-

Table 5 PGSAS score for living status and QOL categories

		Elderly group n=14		Non-elderly group n=24		*P*-value
		mean	SD	mean	SD	
Living status	Change in body weight (%)	-5.3	20.0	-8.6	23.8	0.651
	Amount of food ingested per meal (%)	6.2	2.2	6.0	1.1	0.752
	Necessity of additional meals	2.1	0.5	2.1	0.8	1.000
	Quality of ingestion subscale	2.6	1.1	2.6	1.4	1.000
	Ability for working	2.9	1.3	2.1	1.1	0.061
QOL	Dissatisfaction with symptoms	1.7	0.9	1.7	0.8	1.000
	Dissatisfaction during meals	2.4	1.5	2.1	1.1	0.518
	Dissatisfaction during work	2.0	1.2	1.8	0.8	0.582
	Dissatisfaction with daily life subscale	1.9	1.1	1.9	1.9	1.000

PGSAS, Postgastrectomy Syndrome Assessment Scale; QOL, quality of life

pouch addition to total gastrectomy procedures with Roux-en-Y reconstruction in elderly patients.

According to several studies, there is 10–15% weight loss after total gastrectomy procedures, especially in elderly patients, which is a serious concern that needs to be addressed[1, 5, 8]. The current study indicated no significant difference in the rate of postoperative weight loss between the elderly and non-elderly groups, although the rate of weight loss tended to be lower in the elderly group. We hypothesized that this was because the elderly group tended to have a lower preoperative BMI, so there was no significant difference in weight loss rate between the two groups, although it is said that elderly patients tended to be higher weight loss after surgery because they have various comorbidities and lack reserve capacity. Furthermore, the 1-year rate of change in serum total protein, albumin, and total lymphocyte count (commonly used as nutritional indices after gastrectomy) and PNI (demonstrated to be useful for gastrointestinal surgery) was comparable with that in the non-elderly group. These findings suggest that aboral-pouch addition in Roux-en-Y reconstruction after laparoscopic total gastrectomy is beneficial for elderly patients diagnosed with gastric cancer. However, this result may not be solely due to aboral-pouch addition during surgery but also because patients have been receiving postoperative nutritional guidance, medications, life guidance, and psychiatric care. This study demonstrated that aboral-pouch addition did not cause short-term complications or adverse nutritional effects. These results are similar to those reported previously, where an aboral pouch was proposed to compensate for reduced reservoir capacity. Nutritional indicators, such as total protein, were maintained, which would support such results in higher-risk elderly patients[20, 21].

Tsuji et al. reported that the surgical technique required for aboral-pouch addition to Roux-en-Y reconstruction was not complicated and could be safely performed as the stapler used for reconstruction has evolved from two to three rows[8]. However, we postulate that aboral-pouch creation after total gastrectomy has not become a standard technique partly owing to surgeons' concerns regarding associated complications. Indeed, complications, although infrequent, have been reported, including obstruction due to excessive pouch expansion and pouch necrosis[22, 23, 24]. Our results showed no complications related to the anastomotic site including the aboral pouch. The observation period of this study was approximately 1 year; further follow-up is required to determine possible long-term complications.

We created the Y limb after total gastrectomy extracorporeally because of its maneuverability and simplicity. Although there is an additional cost for a linear stapler, we only used a 60-mm stapler to create the pouch when making the Y-limb. No special, complicated technique was required, and the operative time was not prolonged. The patients in our study did not experience any intraoperative or postoperative aboral pouch-related complications. Hence, this technique should not be avoided

on the basis of complications and surgical technique-related issues.

The difficulty in assessing clinical effectiveness, including parameters such as PGS and QOL, after gastrectomy is due to variability in assessment metrics. The Short Form Health Survey and GSRS are useful but cannot evaluate dumping symptoms or specific meal-related symptoms that occur frequently after gastrectomy[25,26]. EORTC QLQ-C30 and STO-22 have also been developed for the evaluation of QOL in cancer patients undergoing treatment. However, these are not suitable for the assessment of several essential symptoms of PGS[27,28]. PGSAS-37 can comprehensively evaluate PGS and QOL using a self-reported questionnaire for gastric cancer patients who have undergone gastrectomy procedures[7]. This questionnaire contains questions about well-known, specific, and characteristic symptoms that significantly affect the QOL in patients undergoing gastrectomy procedures. Therefore, herein, the PGSAS-37 was used to evaluate PGS and QOL in patients with an aboral pouch created in laparoscopic total gastrectomy Roux-en-Y reconstruction. There were no worse outcomes reported in the elderly patients compared with the non-elderly patients, including esophageal reflux symptoms and various QOL issues that are more likely to occur in elderly patients. Several studies have reported the evaluation of PGS and QOL with aboral-pouch addition after total gastrectomy. Syn *et al.* reported few dumping and esophageal reflux symptoms, large amounts of food intake, and nutritional superiority[29]. Alternatively, Tanaka *et al.* conducted a prospective multicenter observational study of 5-year QOL and nutritional status in patients who underwent abdominal pouch reconstruction after total gastrectomy for gastric cancer and reported no significant aboral pouch-associated complaints other than diarrhea, nutritional indices, and QOL[11]. Although meta-analyses have been conducted on the aboral pouch, there is a possibility that PGS and QOL were not properly assessed. Tsuji *et al* conducted a nationwide multi-institutional cross-sectional study, which suggested that total gastrectomy with the addition of aboral pouch, particularly oral pouches, significantly improved postoperative QOL[8,30]. These reports have led to the coverage of aboral-pouch creation in total gastrectomy by insurance in Japan since April 2022. Consequently, the number of surgeries wherein an aboral pouch is added after gastrectomy is expected to increase in the future. Hence, appropriate postoperative functional assessment of these surgeries is an important issue.

This study has some limitations. First, this was a single-center retrospective observational study with a small sample size. Recently, however, procedures to leave a small remnant stomach and proximal gastrectomy have become popular, and cases of total gastrectomy are decreasing. Under such circumstances, a small number of cases from a single-center would be acceptable. We believe that our data are significant because total gastrectomy is rare. Second, this study assessed outcomes 1 year after total gastrectomy procedures, and long-term follow-up is necessary. However, the nutritional indices, PGS, and QOL investigated herein stabilized at 1 year postoperatively; therefore, no major problems should be expected during the observation period[5]. Third, it was difficult to rationally explain all findings observed. PGS and QOL vary widely among individuals and are influenced by various physical and functional factors. The aboral pouch for Roux-en-Y reconstruction in total gastrectomy is created either on the Roux limb or on the Y limb. However, creation on the Y limb is more common, and our institution does not create an aboral pouch on the Roux limb (oral side). Hence, this was not the subject of the study. Further research is required to determine the appropriate site for pouch creation and the appropriate pouch size.

Total gastrectomy with an aboral Roux-en-Y pouch could be beneficial for elderly patients in terms of postoperative nutritional status, PGS, and QOL.

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Author contributions

AK contributed to the study concept and design; data acquisition, analysis, and interpretation; drafting the manuscript; and performed the statistical anal-

ysis. SY contributed to the study concept and design; data analysis and interpretation; and manuscript revision. YutY, KT, YukY, and SK performed data acquisition. HO, MVB, and TF supervised the study. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

Availability of data and materials

The authors confirm that data supporting the findings of this study are available within the article.

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Original Articles

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Initiation of a *Helicobacter pylori* Screening Program: Enhancing Healthcare at Juntendo University

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Objectives: We started *Helicobacter pylori* (*H. pylori*) screening program of students at Juntendo university in 2020. We report the current status of *H. pylori* screening program and the outcomes of *H. pylori* screening program.
Methods: The students of the School of the Faculty of Health Sciences of Juntendo University enrolling in the spring of 2020–2022 were recruited for this study. The anti-*H. pylori* antibody test was used for detecting *H. pylori* infection. An individual with a serum anti-*H. pylori* antibody titer of less than 3 U/ml was considered to be negative for *H. pylori* infection. If the antibody titer was 3 U/ml or higher, the subject was considered to be possibly infected and recommended to visit a hospital for further testing. Esophagogastroduodenoscopy and 13C urea breath test were performed for diagnosing *H. pylori* infection at the hospital. Eradication therapy was performed, and the eradication assessment were performed at least 8 weeks after the end of eradication therapy.
Results: Seven hundred twenty-eight students were screened for *H. pylori* from 2020 to 2022. Fifty-seven students were recommended to visit a hospital based on the anti-*H. pylori* antibody serum test. Forty-seven students visited Juntendo university hospital. Eleven of the 47 students were positive for *H. pylori* and all of them students received eradication therapy. *H. pylori* eradication was successful in nine of the 11 students.
Conclusions: The *H. pylori* screening program for university students at Juntendo university has been successfully initiated with nine successful eradications since its inception in 2020.

Key words: *Helicobacter pylori*, screening, eradication, university students

Introduction

Helicobacter pylori (*H. pylori*) infection is primarily acquired during childhood and can persist for many years if left untreated[1, 2)]. Although many people infected with *H. pylori* do not experience any symptoms, it can cause a variety of gastrointestinal problems including gastritis, peptic ulcers, and increased risk of gastric cancer[1, 3)].

H. pylori eradication therapy for young people has been shown to be effective as a measure to prevent gastric cancer[4, 5)]. It is important to diagnose whether individuals are infected with *H. pylori* and to provide *H. pylori* eradication therapy to infected individuals.

We have initiated a *H. pylori* screening program

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to detect infection and facilitate its treatment in 2020. Now that several years have passed, we report the current status of *H. pylori* screening program at Juntendo University and the outcomes of *H. pylori* screening program.

Methods

Study design

This study was a retrospective cohort study. The protocol used for this study was reviewed and approved by the Institutional Ethics Committee of the Juntendo University (Approval number: E22-0063).

Subjects

The students of the School of the Faculty of Health Sciences of Juntendo University enrolling in the spring of 2020-2022 were recruited for this study.

Methods

The method for Helicobacter pylori screening

1. Explanation of *H. pylori* screening to the subjects

H. pylori screening instruction manual before *H. pylori* screening were distributed to the students. The instruction manual included information about *H. pylori* infection, the significance of screening, symptoms of infection, screening methods, how to read the screening results, treatment methods, and the benefits of performing *H. pylori* eradication therapy (Supplementary Figure 1).

It was explained that students who do not wish to undergo *H. pylori* screening can refuse to undergo the *H. pylori* screening.

The handout was given to the students with the result of *H. pylori* screening which explains the relationship between *H. pylori* infection and gastric cancer, and the effect of *H. pylori* eradication therapy on the prevention of gastric cancer in different age groups. *H. pylori* eradication therapy has been shown to be highly effective in preventing *H. pylori* infection in the next generation[6] (Supplementary Figure 2).

2. Methods of detecting *H. pylori* infection and criteria for hospital referral

The anti-*H. pylori* antibody test (E-plate Ⅱ 'Eiken' *H. pylori* antibody; Eiken Chemical Co., Ltd., Tochigi, Japan)[7] was used for detecting *H. pylori* infection. Blood samples were obtained during the health check upon admission of students to the school. An individual with a serum anti-*H. pylori* antibody titer of less than 3 U/ml was considered to be negative for *H. pylori* infection. An anti-*H. pylori* antibody titer of 3-10 U/ml was defined as high-negative titer, and that of more than 10 U/ml was defined as positive titer (Figure 1). If the antibody titer was 3 U/ml or higher, the subject was considered to be possibly infected and recommended to visit a hospital for further testing.

Hospital Evaluation and Follow-up Protocols

Esophagogastroduodenoscopy (EGD) and 13C urea breath test (UBT, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) were performed for diagnosing *H. pylori* infection at the hospital. A result of 2.5‰ or above on the UBT was defined as UBT-positive for *H. pylori* infection. *H. pylori* eradication therapy was recommended for individuals who are positive for *H. pylori* infection by the UBT. Students with a result of less than 2.5‰ on the UBT were defined free of *H. pylori* infection, and they were deemed unnecessary for further medical attention (Figure 1).

Eradication therapy and assessment of H. pylori eradication

Eradication therapy consisted of 20 mg vonoprazan, 750 mg amoxicillin, and 200 mg clarithromycin twice a day for 7 days. UBT were performed for the eradication assessment at least 8 weeks after end of therapy.

Results

The number of first-year students of the School of Faculty of Health Sciences who were screened for *H. pylori* from 2020 to 2022 was 728. No student refused to participate in the screening, and the participation rate in *H. pylori* screening among the three incoming classes of students was 100%. Twelve students (1.6%) had a positive titer and 45 students (6.2%) had a high-negative titer. Therefore, a total of 57 students (7.8% of total) were recommended to visit a hospital for further testing. Of these, fifty-six students visited a hospital. Only one student who had a high-negative titer did not visit a hospital. Forty-seven out of the 56 students visited Juntendo University Hospital. Nine of the 47 students were positive for *H. pylori* on the UBT.

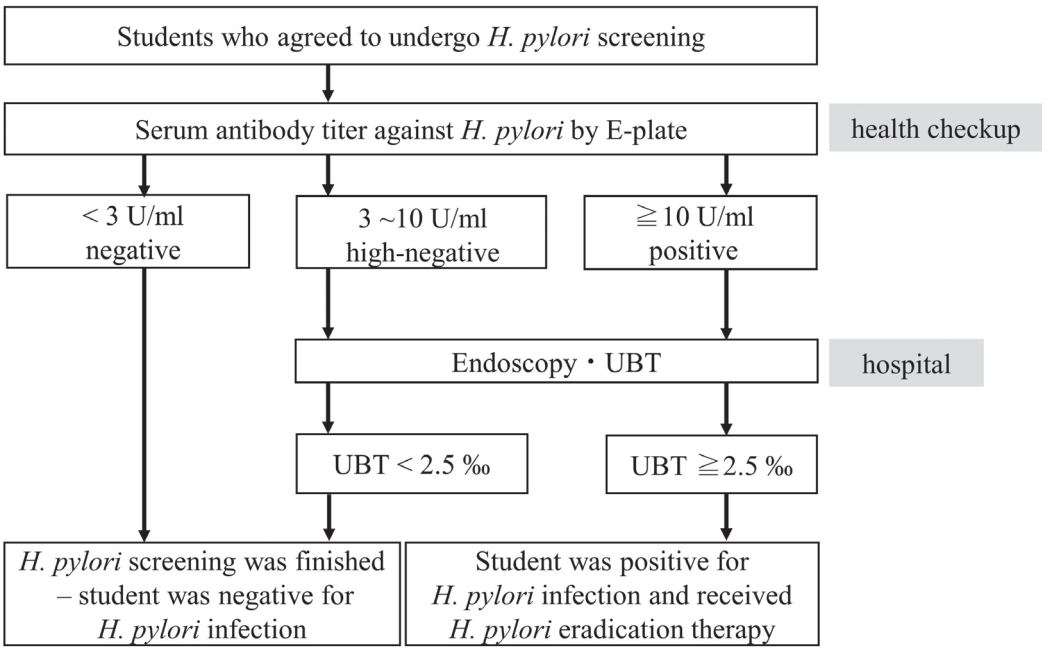

Figure 1 Flowchart of *H. pylori* screening program at Juntendo university
We recommended that students with a serum antibody titer of 3 U/ml or higher be examined at a hospital. They underwent EGD and additional examinations such as the UBT for diagnosing *H. pylori* infection at the hospital. A value of 2.5‰ or above on the UBT indicates that the individual is positive for *H. pylori* infection and should be treated with *H. pylori* eradication therapy.
H. pylori, *Helicobacter pylori*; E-plate, method of detecting serum *H. pylori* antibody; UBT, 13C-urea breath test; EGD, esophagogastroduodenoscopy

These nine students also had positive titers, and all of them underwent *H. pylori* eradication therapy. Two of the 47 students did not undergo UBT based on each doctor's decision. The two students had also positive titer and all of them students underwent *H. pylori* eradication therapy. All students with high-negative titers for serum *H. pylori* antibody were negative on the UBT. *H. pylori* eradication therapy was successful in nine of the 11 students, and it was unsuccessful in one student. The remaining one *H. pylori*-positive student did not visit the hospital after receiving prescriptions for the *H. pylori* eradication therapy (Figure 2). Of the nine students who visited other hospitals, one had a positive titer and underwent eradication therapy. The results of eradication assessment of were not interviewed. Eight of the subjects had a high-negative titer, and all of them are under observation.

Discussion

This report summarized the current status of *H. pylori* screening program held at Juntendo University and the outcomes of the first three years of the screening. *H. pylori* eradication therapy is known to be effective in reducing the risk for gastric cancer[4,5,8]. Therefore, we started *H. pylori* screening program of students to reduce the risk of gastric cancer among Juntendo University students.

No student refused to participate in the screening, and participation rates in the *H. pylori* screening were high from the first year and continued to be high in following years. All but one of the students who were recommended to visit a hospital during the three-year period, even though they had no symptoms, visited a hospital for follow-up testing and treatment, and the initiative completion rate was 98% (56/57). First, we distributed an instruction manual for *H. pylori* screening before *H. pylori* screening (Supplementary Figure 1). The handout explaining the interpretation of the results was distributed to the students with the result of *H. pylori* screening (Supplementary Figure 2).

We believe that our educational activities to inform students of the significance of *H. pylori* screening have been successful. Also, the fact that the target groups of our *H. pylori* screening program were students, who were easy to follow, was one

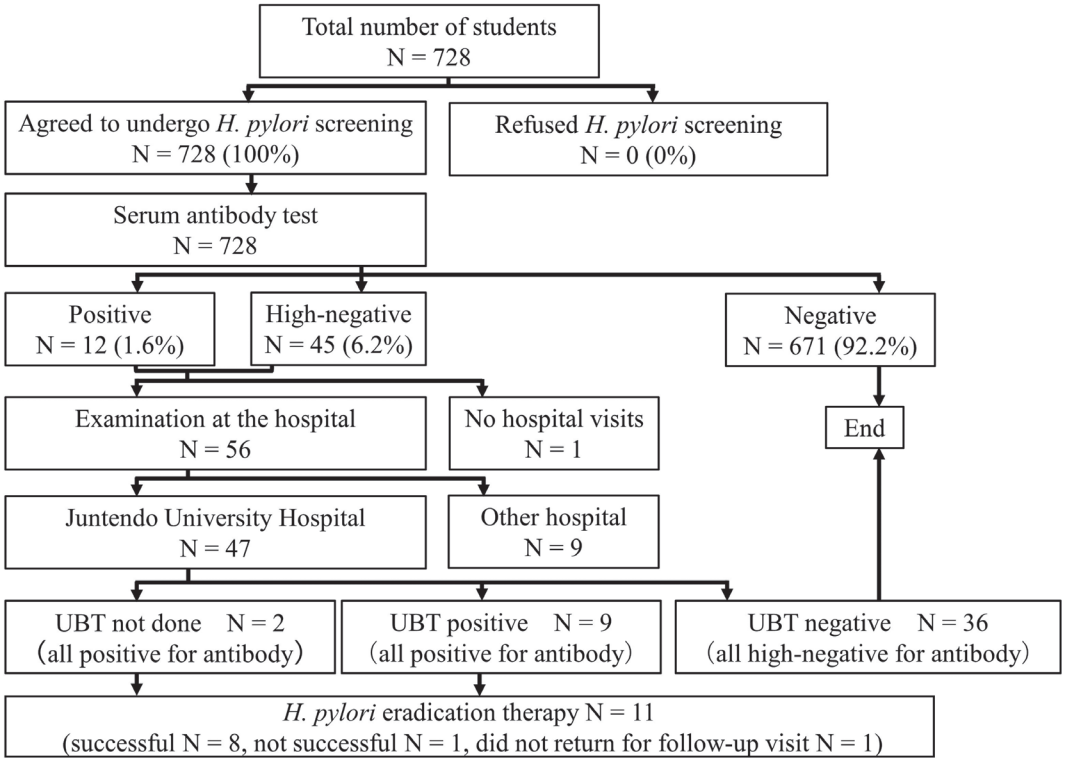

Figure 2 Summary of the results of our *H. pylori* screening program in three incoming classes of students
A total of 728 people in the three incoming classes of students were eligible for screening for *H. pylori*, and all 728 individuals (100%) agreed to undergo screening for *H. pylori* infection. Twelve individuals (1.6%) had a positive titer, while 45 individuals (6.2%) had a high-negative titer. Fifty-six of the 57 students with a positive or high-negative titer visited a hospital for further testing. Forty-seven students visited Juntendo University Hospital, and eleven of those who visited Juntendo University Hospital were positive for *H. pylori* infection and received *H. pylori* eradication therapy. Among the 11 students who underwent *H. pylori* eradication therapy, *H. pylori* was successfully eradicated in 9 students.

factor in the extreme high initiative completion rate.

Our *H. pylori* screening program is intended for university students, who range in age from 18 to 30 years old. Most of the target population are young. Some reports suggest that eradication therapy is effective at all ages[4, 9]. Whether or not *H. pylori* screening will reduce the number of gastric cancer cases, reduce the number of *H. pylori*-infected individuals in the next generation, and reduce the incidence of *H. pylori*-related diseases such as gastroduodenal ulcers, will become evident through long-term observation of the outcomes following the initiation of this program. Furthermore, we believe that continuing *H. pylori* screening program not only will lead to a lower risk of gastric cancer and a reduction in the number of people infected with *H. pylori* in the next generation, but also will provide information on the incidence of *H. pylori* infection, especially among young people.

The positive predictive value of the urinary anti-*H. pylori* antibody tests was 61.2%, suggesting the presence of false positives[10]; therefore, we measured the serum antibody titer against *H. pylori*. With the E-plate II 'Eiken' *H. pylori* antibody test, uninfected subjects have a test result of less than 3 U/ml, but a small number of individuals with present infection have a high-negative titer[11, 12]. Therefore, we recommended that individuals with serum antibodies of 3 U/ml or higher visit a hospital for further testing and treatment for positive cases. However, in this study, 36 high-negative students were UBT negative. Toyoshima et al. reported that 17% of cases with high-negative titers between 3 U/ml and 10 U/ml were positive on the UBT[11]. The positive rate on the UBT among individuals with an antibody titer of less than 3 U/ml is reported to be 0.3%[12], and we decided to continue to recommend that individuals with an antibody titer of 3 U/ml or higher visit a hospital for further testing using a test method with high sensitivity for a few more

years. According to future results, we might raise the antibody titer threshold at which we recommend that individuals visit a hospital for further testing. We began targeting first-year university students, and we have not been asking individuals whether they had a history of receiving *H. pylori* eradication therapy in the past. However, there are already reports of young patients receiving *H. pylori* eradication therapy[13-16], and some university students may have already received *H. pylori* eradication therapy. In order to avoid unnecessary tests in the future, it is necessary to interview individuals to determine whether they had received *H. pylori* eradication therapy in the past. Follow-up strategies for those who were detected *H. pylori* infection and have been treated with eradication have not yet been determined. This matter represents a crucial area for future research.

In conclusion, the *H. pylori* screening program for university students at Juntendo University has been successfully initiated, with high participation rates since its inception in 2020. A longer observation period is needed to assess whether this screening program can reduce the gastric cancer rate and whether it can reduce the number of *H. pylori*-infected individuals in the next generation. We should further expand the target population and examine the results in the future.

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Author contributions

KU and AN designed the study. KU, KI, HF, and TN considered of operational methods. KI prepared for performing the study. KU analyzed and interpreted the data. KU and MH drafted and revised the manuscript. KU, SO, TT, YA and HU conducted a medical examination on the target patient. All authors reviewed the manuscript and approved the final version of the manuscript.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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ヘリコバクターピロリ検診
～順天堂大学 胃がん撲滅運動～

ヘリコバクターピロリ（ピロリ菌）って何？！

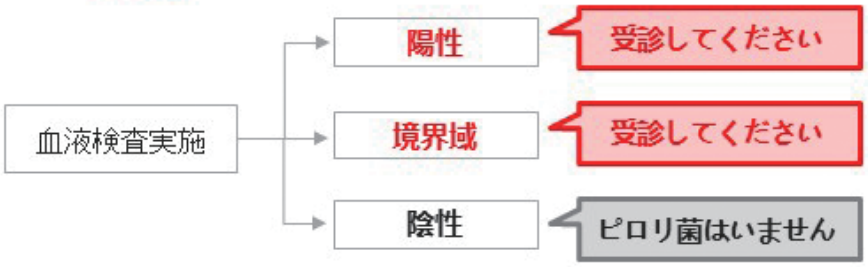
ピロリ菌はヒトの胃粘膜に生息しています。
経口感染すると言われており、親が感染者であると**子供にうつる可能性があります。**
持続感染すると胃がん発症の確率は高くなります。
よって若いうちにピロリ菌を除菌することが理想とされています。

みなさんの除菌治療は、自分自身のためだけでなく
次世代への感染対策として有効です

ピロリ菌除菌治療について

学部生健康診断の際、ヘリコバクターピロリ検診を実施します。

- 感染の症状　：多くの場合症状はありません。
- 検査方法　：血液中に存在する抗体を測定します。
- 検査結果　：「**陽性**」「**境界域**」と判定された場合、医療機関を受診してください。
  「**陽性**」の場合、除菌治療をしましょう。
  「**境界域**」の場合、追加検査を行い、治療が必要か医師の判断が必要です。



- 治療方法　：年度内に順天堂医院に受診される場合、医療費の減免が適応されます。
  ① ピロリ菌が原因の病変があるかを調べるため胃内視鏡検査をします。
  ② ピロリ菌除菌治療 **抗生物質・胃薬を7日間内服し除菌**します。
  ③ 除菌後判定
  ④ 判定結果による今後の方針説明
- 除菌のメリット：ピロリ菌感染が原因の胃・十二指腸潰瘍や**胃がんの予防効果**があります。

＜注意事項＞
・ヘリコバクターピロリ抗体価採血を希望しない方は、健診受診時に申し出てください。
・この検査で陰性と判定されても、ピロリ菌が100％いないということではありません。

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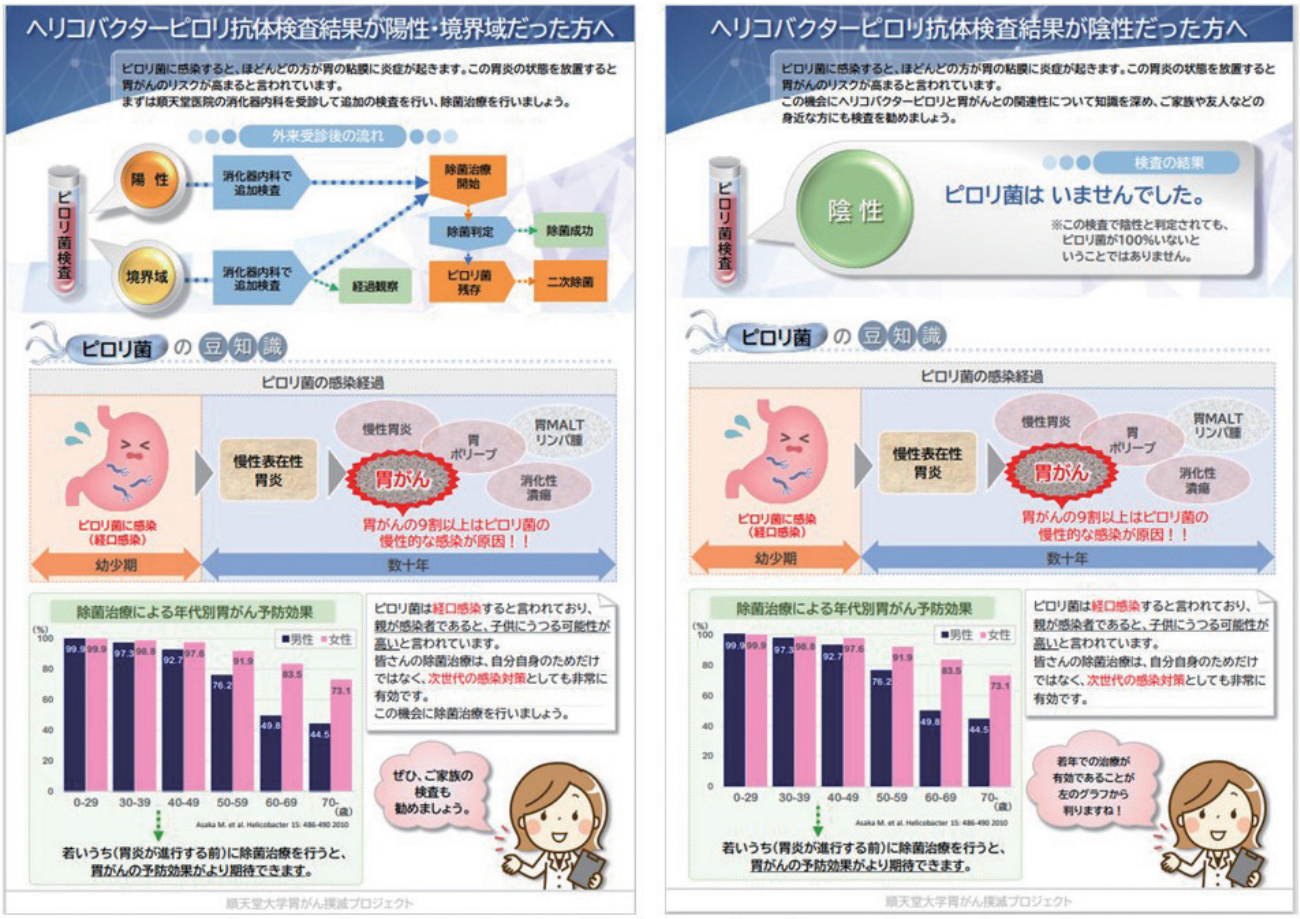
Supplementary File1. *H. pylori* screening instruction manual

The instruction manual included information about *H. pylori* infection, the significance of *H. pylori* screening, symptoms of infection, screening methods, how to read the screening results, treatment methods, and the benefits of performing *H. pylori* eradication therapy.



Supplementary Figure 2. A brochure describing interpretation of the *H. pylori* screening results.

Perspectives

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Activity of a Medical Relief Team from Shizuoka Hospital that was Dispatched to the Noto Peninsula Earthquake in Reiwa 6 (2024)

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Objective: The present study aimed to report on the activity of a medical relief team from Juntendo Shizuoka Hospital that was dispatched to the Noto Peninsula Earthquake in Reiwa 6.

Design: Narrative report.

Results: The activities conducted on-site in the Noto Peninsula involved multiple deployments of the Juntendo University Shizuoka Hospital Disaster Medical Assistance Team (JS-DMAT). The first deployment from January 2nd to January 6th faced challenges due to damaged infrastructure, particularly roads, affecting mobility. The team focused on hospital medical support, patient transportation, and DMAT headquarters assistance. The second deployment, from January 8th to January 12th, encountered persistently damaged roads, leading to incidents but no significant vehicle damage. The team engaged in screening, zoning, medical examinations, and DMAT headquarters support in evacuation shelters. The third team's planned activities in early February were canceled by Shizuoka Prefecture.

Additionally, on January 7, 2024, personnel from Juntendo Shizuoka Hospital participated in the Shizuoka Prefectural DMAT Coordination Headquarters activity, documenting DMAT activities and assessing team members' health. The Ministry of Health, Labour and Welfare's request for the fourth Shizuoka Prefecture DMAT dispatch led to the selection of the second JS-DMAT for deployment.

Conclusion: The activities related to the Noto Peninsula earthquake by JS-DMAT were reported. Lessons from this disaster are being sought to guide future disaster response preparations.

Key words: medical relief team, Noto, earthquake

Introduction

On January 1, Reiwa 6, at 16:10, the Noto Peninsula Earthquake with an estimated magnitude of 7.6 occurred. This seismic event resulted in an expansion of approximately 4.4 square kilometers of land towards the sea within a range of about 90 kilometers on the northern side of the Noto Peninsula[1]. The maximum coseismic displacement was observed in Wajima City, Ishikawa Prefecture, measuring approximately 240 meters. Furthermore, the ground uplift in Wajima City reached a maximum of 3.9 meters, marking the most significant uplift in the past 6,000 years[1]. The earthquake was characterized by a seismic intensity of 7 in Shika Town, Ishikawa Prefecture, and coastal areas experienced tsunamis, causing widespread damage. As of February 28, 2024, it has been confirmed that there

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were more than 241 fatalities, over 1,540 injuries, and damage to over 77,703 residences due to this seismic event.

The Ministry of Health, Labour and Welfare requested the dispatch of Disaster Medical Assistance Teams (DMAT) to the central region on January 2, 2024, including Shizuoka Prefecture, in response to the Noto Peninsula Earthquake. The DMATs are mobile, trained medical teams that can be rapidly deployed during the acute phase of a sudden-onset disaster[2]. The Shizuoka prefecture government requested the dispatch of Shizuoka DMATs. The Juntendo Shizuoka DMAT (JS-DMAT) responded to a request from the Shizuoka prefecture government. We hereby present the actions taken by JS-DMAT in response to the Noto Peninsula Earthquake in Reiwa 6.

Report

Shizuoka University Hospital, affiliated with Juntendo University School of Medicine, carried out DMAT related activities in response to the Noto Peninsula Earthquake, commissioned by the Shizuoka Prefectural Government. These activities can be broadly classified into three main categories. Firstly, there were those who were dispatched to the Noto Peninsula earthquake-affected area and engaged in on-site operations. Secondly, there were activities coordinated at the Shizuoka Prefectural DMAT Coordination Headquarters. The last category involved medical helicopter operations in the eastern part of Shizuoka Prefecture.

(1) Activities conducted on-site in the Noto Peninsula

a. The First Juntendo University School of Medicine Affiliated Shizuoka Hospital DMAT Activity (Figure 1)

The first dispatch of the Juntendo University School of Medicine Affiliated Shizuoka Hospital DMAT (Disaster Medical Assistance Team) took place from January 2nd to January 6th. The chronological details of this activity are summarized in Table 1. The operation faced challenges due to significant damage to key infrastructure, particularly roads and sewage systems, among the lifelines in the disaster-stricken area. The notable deterioration of roads posed substantial difficulties for mobility, consuming considerable time. The team primarily engaged in hospital medical support (Figure 2), patient transportation, and support for the DMAT headquarters in the affected area.

b. The Second Juntendo University School of Medicine Affiliated Shizuoka Hospital DMAT Activity (Figure 3)

The second deployment of the Juntendo University School of Medicine Affiliated Shizuoka Hospital

Figure 1 The First Juntendo University School of Medicine Affiliated Shizuoka Hospital DMAT (JS-DMAT)
The first JS-DMAT was consisted of one physician, two nurses, and two logistics personnel.
DMAT, Disaster Medical Assistance Team

Table 1 Activities of the First Juntendo Shizuoka DMAT

Dates and times	Contents of activities
2024/1/2 19:27	The Juntendo DMAT team departed with one DMAT vehicle and one ambulance.
2024/1/3 0:10	They stayed overnight in Gunjo City, Gifu Prefecture.
2024/1/3 5:58	Upon leaving the accommodation, they encountered a road closure for general vehicles beyond the Takaoka interchange on the Noto Expressway. The team manually moved cones to pass through.
2024/1/3 9:20	Upon arrival at Noto General Hospital (Headquarters for Noto Medical Care Area Activities), they found a chaotic situation with confusion in information and inadequate coordination with administrative and health authorities. The directive for deployment to the arriving DMAT could not be executed. While electricity was available, there was a continuous water outage. The toilet conditions were severe, with overflowing waste, prompting the team to use standby time to initiate improvement activities.
2024/1/3 12:58	They began investigating the damage situation in the Noto medical care area and updating the report form.
2024/1/3 14:10	Patient transport for a femoral neck fracture was requested to Ishikawa Prefectural Central Hospital. Some team members remained at the headquarters to continue supporting operational tasks.
2024/1/3 15:38	Patient transport commenced.
2024/1/3 16:39	They originally planned for Ishikawa Central Hospital. However, the destination was changed to Kanazawa University Hospital, leading to a change in the route.
2024/1/3 16:56	Upon arrival at Kanazawa University Hospital, the team faced a shortage of gasoline, resulting in a few hours spent searching for a gas station in Kanazawa.
2024/1/4 6:02	The team members who conducted transports in the same area stayed overnight. They then departed for Noto General Hospital.
2024/1/4 6:53	They arrived at their destination.
2024/1/4 9:01	The dispatch of four teams from Juntendo Shizuoka Hospital DMAT, led by the leader, was decided. The teams were set to go to Wajima General Hospital via Anamizu General Hospital, with Gifu Prefectural General Medical Center, Yamanashi Prefectural Central Hospital, and Shizuoka Red Cross DMAT. During this dispatch, it was also decided that the transportation of insufficient supplies and food would be carried out in addition.
2024/1/4 10:02	Departing from Noto General Hospital, the roads to Anamizu were frequently blocked, requiring assistance from the Ministry of Land, Infrastructure, Transport and Tourism, the Self-Defense Forces, and the police. The team proceeded towards their destination with the help of these forces.
2024/1/4 13:27	After arriving at Anamizu General Hospital and leaving supplies, the team departed for Wajima General Hospital. The journey to Wajima General Hospital was challenging, with severe road damage, collapsed houses, and landslides blocking the way. The team encountered life-threatening situations due to falling rocks and debris from collapsed houses. There were numerous areas with the risk of tire bursts, and they had to traverse cracked roads multiple times. The normally 2-hour journey took over 7 hours, and they reached their destination in the evening. The road they traveled was the only passage, repeatedly affected by road collapses and landslides. This mission posed the risk of being unable to return in case of road closures due to aftershocks or rainfall. The situation required meticulous attention to avoid tire punctures.
2024/1/4 15:45	Arrived at Wajima General Hospital. The hospital did not experience a power outage, and though there was a water cut, water supply was still available. The major issue at the hospital was related to toilets due to problems with the sewage system. While the hospital managed to provide emergency care, continuing hospitalization was challenging. As a result, patients eligible for hospitalization were being transferred to other medical facilities as needed. At Wajima Hospital, staff who had been on duty on New Year's Day continued working until the 4th. Despite their homes being damaged, the staff continued their duties without returning home. The surrounding evacuation centers were also in poor conditions, and the situation was challenging for both the city and the health department. Confirming the safety of residents in collapsed houses was almost impossible at that time.
2024/1/4 16:30	They attended a meeting, and as a result, it was decided that they would be responsible for the overnight emergency room while taking breaks for rest. They were able to conduct CT scans using a self-power generator, but the images couldn't be confirmed on the electronic medical record. Therefore, they performed the image interpretation in the CT examination room. They handled cases such as suturing, treating burns from prolonged application of hot packs in evacuation centers, and managing a clavicle fracture resulting from a fall in a precarious location. Due to the unavailability of the electronic medical record system, I documented alternative information to referral letters.
2024/1/5 8:00	They participated in a meeting and received a request for the transfer of a patient with diabetic ketoacidosis. To ensure space for patient transport, they donated essential items from the carried equipment that were needed in the disaster-stricken area. When a request for accommodating a patient with diarrhea came in, and considering the unavailability of functional toilets, they provided a portable, seated toilet brought from our hospital to meet the specific needs of the situation.
2024/1/5 11:22	Patient transport to Ishikawa Prefectural Central Hospital was initiated.
2024/1/5 15:31	Arrival at Ishikawa Prefectural Central Hospital.
2024/1/5 16:10	After completing the patient transport, the conclusion of the transfer was reported to Noto General Hospital. The team received instructions to withdraw from the headquarters.
2024/1/5 18:28	Stayed overnight in Himi City.
2024/1/6 7:30	Departure from the accommodation.
2024/1/6 15:15	Returned to Juntendo Shizuoka hospital.

DMAT, Disaster Medical Assistance Team

Figure 2 The First Juntendo University School of Medicine Affiliated Shizuoka Hospital DMAT Activity
The photo depicts a scene of medical services being conducted at a disaster response hospital.
DMAT, Disaster Medical Assistance Team

Figure 3 The Second Juntendo University School of Medicine Affiliated Shizuoka Hospital DMAT (JS-DMAT)
The second JS-DMAT was consisted of one physician, three nurses, and one logistic personnel.
DMAT, Disaster Medical Assistance Team

DMAT took place from January 8th to January 12th. The chronological details of this activity are outlined in Table 2. Similar to the first deployment, the operation faced challenges due to persistently damaged roads in the disaster-stricken area. There were incidents of wheel dislocation during night-time travel, attributed to encountering rockfall and difficult snow-covered roads. Fortunately, the vehicle sustained no significant damage. The team primarily engaged in activities such as screening (Figure 4), zoning, medical examinations, and support for the DMAT headquarters in evacuation shelters in the affected region.

Table 2 Activities of the Second Juntendo Shizuoka DMAT

Dates and times	Contents of activities
2024/1/8 9:05	Received the fourth deployment order and began preparations.
2024/1/8 12:10	Departed from Juntendo University School of Medicine, Shizuoka Hospital.
2024/1/8 21:30	Arrived at the accommodation in Takaoka.
2024/1/9 5:55	Departed from the accommodation.
2024/1/9 7:33	Arrived at Noto General Hospital, the base of operations.
2024/1/9 8:30	Departed from Noto General Hospital towards the Wajima City Hall, combining material transport.
2024/1/9 12:03	Arrived at the Health, Medical, and Welfare Coordination Headquarters within Wajima City Hall.
2024/1/9 13:50	Initiated activities by dividing into two groups for shelter support and assistance to the headquarters. Conducted medical examinations for 8 individuals with health issues at Kawai Elementary School. At Najimi Evacuation Center (Community Center), performed screening for 400 individuals (2 with fever, 2 with diarrhea, and 1 requiring treatment for a hand injury) and provided medical examinations.
2024/1/9 21:19	Concluded medical examinations and screening. Started moving towards the accommodation. On the way back, the team encountered challenges such as the vehicle riding over fallen rocks and a wheel detaching, but the team worked together to resolve the issues.
2024/1/10 0:36	Arrived at the accommodation in Wajima City.
2024/1/10 7:56	Departed from the accommodation.
2024/1/10 8:11	Received requests for screening at evacuation centers.
2024/1/10 8:51	Split into two teams and departed from Wajima City Hall towards Mitsui Community Center and Noto Airport Aid Station.
2024/1/10 10:38	Arrived at Noto Airport Aid Station and began screening for 30 evacuees.
2024/1/10 11:43	Concluded screening at Noto Airport Aid Station and departed for Mitsui Community Center.
2024/1/10 13:28	Arrived at Mitsui Community Center. Started screening for 80 evacuees and conducted examinations for those with symptoms such as fever and vomiting.
2024/1/10 15:10	Concluded activities at Mitsui Community Center Evacuation Center.
2024/1/10 16:00	Arrived at Wajima City Hall.
2024/1/10 16:35	Departed from Wajima City Hall towards Houshi Elementary School Evacuation Center.
2024/1/10 16:48	Arrived at Houshi Elementary School Evacuation Center with 211 evacuees. Due to the increasing trend of respiratory infections, zoning was implemented. There were 9 positive cases for influenza, 12 positive cases for COVID-19, and 1 case positive for both.
2024/1/10 21:50	Concluded activities and departed for Wajima City Hall.
2024/1/10 22:05	Arrived at Wajima City Hall.
2024/1/10 22:20	Departed from Wajima City Hall to the accommodation in Wajima City.
2024/1/10 22:42	Arrived at the accommodation.
2024/1/11 7:42	Departed from the accommodation.
2024/1/11 7:53	Arrived at the Operational Base within Wajima City Hall.
2024/1/11 9:53	Split into two groups; one went to Mitsui Community Center for zoning, and the other to Monzen Community Center for screening. Departed from Wajima City Hall.
2024/1/11 11:18	Arrived at Mitsui Community Center. Two individuals with fever and several with cold symptoms were identified. Those with fever were isolated and moved to other facilities. Health nurses and infection control nurses were dispatched to the facility for information sharing. Completed zoning and moved to Monzen Community Center.
2024/1/11 12:20	Arrived at Monzen Community Center, joined with the other group, and conducted screening at evacuation centers in the Monzen area. Two individuals with fever among evacuees at Monzen Community Center requested examination. The results confirmed both were positive for influenza. Conducted screening at Fukada Assembly Hall and Nishinakao Evacuation Center in the Monzen district.
2024/1/11 16:13	After completing screening at the planned locations, departed for the Health, Medical, and Welfare Coordination Headquarters.
2024/1/11 17:23	Arrived at Wajima City Hall.
2024/1/11 18:30	Attended a regular meeting.
2024/1/11 19:48	Concluded today's activities. This deployment is now completed.
2024/1/11 22:50	Arrived at the accommodation in Takaoka.
2024/1/12 9:00	During this mission, there were incidents involving wheel detachment and rockfall, so an automobile company in the city were inspected.
2024/1/12 10:15	Departed for Juntendo Shizuoka Hospital.
2024/1/12 17:31	Returned to Juntendo Shizuoka hospital.

DMAT, Disaster Medical Assistance Team

Figure 4 The Second Juntendo University School of Medicine Affiliated Shizuoka Hospital DMAT Activity
The photo captures a scene of a meeting discussing screening procedures at an evacuation center.
DMAT, Disaster Medical Assistance Team

c. The Third Juntendo University School of Medicine Affiliated Shizuoka Hospital DMAT Activity

The third team, initially scheduled to commence operations in early February, received notice from Shizuoka Prefecture on January 23rd that the DMAT dispatch would be canceled because the Ministry of Health, Labour and Welfare was unable to forecast the demand for support by DMAT in the Noto Peninsula earthquake. As a result, the planned activities for the third team were canceled.

(2) The Shizuoka Prefectural DMAT Coordination Headquarters activity (Figure 5, Table 3)

On January 7, 2024 (Saturday), as per the request from Shizuoka Prefecture, medical and logistics personnel in Juntendo Shizuoka Hospital participated in the Shizuoka Prefectural DMAT Coordination Headquarters activity. The objectives of this activity included documenting and understanding the activities of the DMAT dispatched from Shizuoka Prefecture and assessing the health status of the team members.

On the same day, the Ministry of Health, Labour and Welfare issued a request for the fourth dispatch of Shizuoka Prefecture DMAT. In response, contacts were made with disaster base hospitals within Shizuoka Prefecture to determine and finalize the DMAT teams to be dispatched. The team from Juntendo University School of Medicine Affiliated Shizuoka Hospital DMAT, which was the second dispatch team, was among those selected for deployment.

(3) The Shizuoka Prefecture Eastern Doctor Helicopter

On January 3, 2024, Ishikawa Prefecture made a support request to Shizuoka Prefecture based on the basic agreement regarding wide-area collaboration in the event of a large-scale disaster, specifically related to doctor helicopter assistance. Shizuoka Prefecture is equipped with two doctor helicopters, with the Shizuoka Prefecture Eastern Doctor Helicopter using our hospital as its base facility. The Shizuoka Prefecture Eastern Doctor Helicopter ranks second nationally in terms of patient transportation among the 56 doctor helicopter bases, consistently having lower deployment numbers due to the high patient transport volume. On the other hand, the number of dispatches for the Shizuoka Prefecture Western Doctor Helicopter is approximate one-fifth of that in the eastern part, ranking it among the lowest in the area among Doctor Helicopter bases. This is because there are five functioning emergency medical centers in western Shizuoka Prefecture, and the transportation of emergency patients by land is sufficient. In contrast, in the eastern part, there is only one functioning emergency medical center at our hospital,

Figure 5 Scene at the Shizuoka Prefectural DMAT Coordination Headquarters One doctor and one logistic personnel
One physician from Juntendo University School of Medicine Affiliated Shizuoka Hospital's DMAT (JS-DMAT), serving as the head of the team, along with three logistics personnel (including one from the JS-DMAT) participated in support operations for several Shizuoka DMATs, dispatched to the Noto Peninsula Earthquake. This took place at the Shizuoka DMAT Coordination Headquarters, where they collaborated with local government officials.
DMAT, Disaster Medical Assistance Team

Table 3 The activity of Shizuoka Prefecture DMAT Coordination Headquarters

Dates and times	Contents of activities
2024/1/7 8:40	Arrival at Shizuoka Prefectural Government Office
2024/1/7 8:45	Arrival at the Shizuoka Prefectural Government
2024/1/7 9:00	DMAT Coordination Headquarters Morning routine meeting at the Shizuoka Prefectural Government
2024/1/7 9:10	DMAT Coordination Headquarters Information gathering regarding the DMAT activities dispatched by Shizuoka Prefecture for the Noto Peninsula earthquake
2024/1/7 12:38	Shizuoka Prefecture received a dispatch request for the third team of DMAT from the Ministry of Health, Labour and Welfare, and coordinated the dispatched DMAT.
2024/1/7 17:45	Evening routine meeting at the Shizuoka Prefectural Government DMAT Coordination Headquarters
2024/1/7 19:30	Withdrawal

DMAT, Disaster Medical Assistance Team

and the frequent use of Doctor Helicopters for transporting emergency patients from distant locations is reflected.

In response to the request, the Shizuoka Prefecture Western Doctor Helicopter, which is also geographically closer to Ishikawa Prefecture, was dispatched to provide support. To cover the vacuum created by the Western Doctor Helicopter's deployment, the Eastern Doctor Helicopter extended its coverage to include the western region. Notably, during the period when the Western Doctor Helicopter was assisting in Ishikawa Prefecture, there were no requests for doctor helicopter support from the western region of Shizuoka Prefecture.

Discussion

JS-DMAT's operational challenges approximately 1.5 days after the disaster onset included difficulties in local access due to disrupted lifelines, particularly the challenges of vehicular movement caused by road damage, problems in waste disposal due to sewage system destruction, and communication disruptions. In the midst of these extensive damages, providing appropriate medical care requires a

comprehensive approach that goes beyond medical specialization. Dealing with such situations necessitates not only medical preparedness but also coordinated efforts involving various organizations[3]. Indeed, what is crucial for acute-phase disaster healthcare is not just medicine itself, but rather collaborative efforts through integrated organizational structures[4].

The primary issue arose from the difficulty in collecting information from evacuation centers due to communication breakdowns. Additionally, direct on-site information gathering was hindered by road damage, especially in areas where the extent of road damage was severe, making information collection impossible. While aerial approaches are an option when land routes are challenging for information gathering, the Noto region, where the disaster occurred, faced obstacles due to low-hanging clouds and adverse weather conditions, exacerbated by the short daylight hours and heavy snowfall in January[5].

On the medical front, the focus shifted from the peak period of acute trauma response in the ultra-acute phase to addressing acute illnesses, including infectious diseases among evacuees living in shelters, and understanding the overall health status, similar to a previous report[6]. Trauma cases from falling objects and collapsed houses primarily peaked within the first 24 hours of the ultra-acute phase. Since JS-DMAT arrived on-site 1.5 days after the disaster, there was no significant need for trauma care.

The Noto Peninsula, already a sparsely populated area with an aging population, now faces significant disruption to lifelines due to a seismic event, especially with an expected prolonged restoration period for water and sewage systems. Consequently, secondary evacuations to unaffected areas are underway due to numerous individuals unable to return home from evacuation centers. The Izu Peninsula, where JS-DMAT is based and shares similar topography with the Noto Peninsula, is using this disaster as a lesson to explore future disaster response preparations[7].

Regarding the dispatch of personnel from our hospital during the acute phase of the Noto Peninsula earthquake, the dispatched staff sacrificed their New Year holidays and vacations to engage in DMAT activities. The impact of scheduling adjustments affected not only the dispatched personnel but also the staff remaining at the hospital, but they supported relief efforts indirectly by helping each other. Our hospital is the last stronghold of emergency medical care in eastern Shizuoka Prefecture, and during this disaster dispatch period, we continued to accept emergency cases as usual, with an ambulance refusal rate of less than 1%, which is normal. For this dispatch, the personnel costs, fuel expenses, and allowances for medications used by the dispatched staff are covered under the Disaster Relief Act.

Conclusion

The activities related to the Noto Peninsula earthquake by JS-DMAT were reported. Lessons from this disaster are being sought to guide future disaster response preparations.

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Author contributions

IT, YN, KH, MI, DA, ST, MS, HK, YN AK and HO were supervised the work, and YY was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Reviews

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Revolutionary Advances of Robotic Surgery in Urology Field

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The advent of robotic surgery has significantly impacted various surgical fields, particularly urology, gynecology, general surgery, and cardiac surgery. While the da Vinci robotic platform has been predominant over the past two decades, recent years have witnessed the emergence of new robotic platforms in Japan, now actively used in clinical practice. Currently, the available systems in Japan, alongside the da Vinci, include the Hinotori, Senhance, Hugo Ras, and Saroa surgical systems. This review focuses on comparing the notable functions of each system in urologic surgery, emphasizing the areas in which they differ from the da Vinci robotic platform. The development of new robotic systems is ongoing, promising not only cost reductions but also the introduction of innovative devices and educational systems. Soft robotics, which constructs robotic devices using soft, adaptable materials, has the potential to become central to the next generation of robotic surgery. Moreover, the collaboration between Artificial Intelligence (AI) and robotic surgery significantly contributes to increasing efficiency, accuracy, and safety in the medical field, with more innovative applications expected in the future.

Key words: robotic surgery, da Vinci, hinotori, urology

Introduction

In laparoscopic surgery, trocars with diameters ranging from 5 to 12 mm are inserted into the abdominal or retroperitoneal cavity. Carbon dioxide is insufflated to expand the abdominal cavity, allowing the necessary instruments to be inserted through the trocar ports for the operation. Compared to open surgery, laparoscopic surgery typically results in smaller surgical wounds, reduced blood loss, and shorter hospital stays. It can be performed either directly by the surgeon or with robotic assistance. However, surgeon-assisted laparoscopy has limitations such as restricted hand movements and limited maneuverability. The introduction of robotic systems marked a significant turning point in the field of surgery. Although conventional laparoscopic surgery, emerging since the 1980s, demonstrated the benefits of a minimally invasive approach, it had major drawbacks: limited movement confined to wrist rotation, minimal rotation at the forceps tip, and the absence of joint-moving instruments. These constraints made tasks like intracorporeal suturing extremely challenging. Consequently, training in laparoscopic surgery involved a steep learning curve, prolonging the training period for future surgeons and hindering the widespread adoption of laparoscopic techniques in the general medical community. In addition, the issues associated with scopists (doctors who operate the endoscope) in laparoscopic surgery can significantly affect the success of the surgery. When communication between the surgeon and the scopist is insufficient, it can lead to inadequate visualization during surgery. Close communication between the two is necessary to provide the precise field of view that

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the surgeon requires. There is also individual variation in the skill level of scopists, and a lack of experience or training can decrease the efficiency and safety of the surgery. Especially in complex surgeries, the skill of the scopist can directly impact the outcome of the surgery. During long surgeries, scopists can accumulate fatigue, which can lead to a decrease in attention and impairment in judgment, potentially leading to mistakes in operation. To address these issues, it is important to provide continuous education and training to enhance the professionalism of scopists, improve communication skills between surgeons and scopists, and strengthen the teamwork of the entire surgical team.

Robot-assisted laparoscopic surgery enables surgeons to operate using a robotic arm and console. Its advantages include high-precision operability and the amplification of the surgeon's fine hand movements, allowing for precise surgical procedures. Additionally, the surgeon can conduct operations with a highly flexible robotic arm inserted into the body cavity while observing three-dimensional endoscopic images on a console situated away from the patient. This setup provides a realistic view of organs and tissues. Robotic surgery reduces surgical complications such as bleeding, preserves organ function, and ensures more reliable anastomoses[1]. In Japan, most procedures that can be performed laparoscopically are now covered by insurance in the field of urology. Indeed, at our facility, we have conducted robotic surgery for prostate cancer, bladder cancer, and renal cell carcinoma, and have reported achieving favorable results[2–6].

While the da Vinci robotic platform has dominated the field of robotic surgery for the past two decades, recent years have seen the introduction of new robotic systems into clinical practice. Five new robotic systems have been commercialized and approved for clinical use in Japan, each designed to address the technical or cost limitations of the da Vinci platform. Currently available robotic systems in Japan include da Vinci, Hinotori, Senhance, Hugo Ras, and the Saroa Surgical System (Figure 1). Additionally, there is the ANSUR 'collaborative assistant robot,' which specializes in assisting roles[7].

This review specifically focuses on the evolution and impact of these systems in the field of urology. With the development of Artificial Intelligence (AI) and further deepening of medical-engineering integration, robot-assisted devices including soft robotics have made significant progress, and their applicability in clinical practice is expected to continue expanding in the future.

New multiport robotic surgical systems

The integration of robotics in surgery, driven by their capability for remote control and precision in repetitive tasks, has evolved over the past 50 years. Although the concept originated over five decades ago, practical application in surgery only began in the late 1980s[8]. The da Vinci system, an endoscopic surgical support robot developed by Intuitive Surgical Inc. in the U.S., comprises three robotic arms, a laparoscope, and an operating console. The console also includes a pedal unit for various energy uses, such as monopolar and bipolar surgery, sealing devices, and automatic anastomosis devices. Approved by the U.S. Food and Drug Administration (FDA) in July 2000, the da Vinci system has undergone several upgrades (Figure 1). Currently, with quarterly revenues of $1.56 billion, Intuitive Surgical holds approximately 80% of the global market share for surgical robots[9].

The da Vinci S model (2006) featured 3D high-definition camera vision, a simplified setup, and an interactive touch-screen display. Three years later, the Si model introduced dual console surgery and adopted firefly technology for real-time fluorescence imaging, enhancing tumor resection visualization[10]. The Xi model boasts a redesigned patient cart for maximum mobility and flexibility, with a boom-mounted structure for docking from any angle and improved access around the patient. The arms have a wider internal range of motion, enhanced patient access, and reduced external collision interference. The Xi model also features compact flex joints for minimal arm interference and optimized arm positioning. Its 8mm endoscope provides lighter, brighter, and higher-resolution images. The da Vinci SP, a single-port surgical platform, facilitates varied surgical access with minimal arm interference and offers cosmetic benefits with smaller surgical wounds. The introduction of various da Vinci models in Japan has progressed rapidly since 2013. By 2023, 569 robots have been installed (Figure 2). However, the high purchase and maintenance costs of the da Vinci system

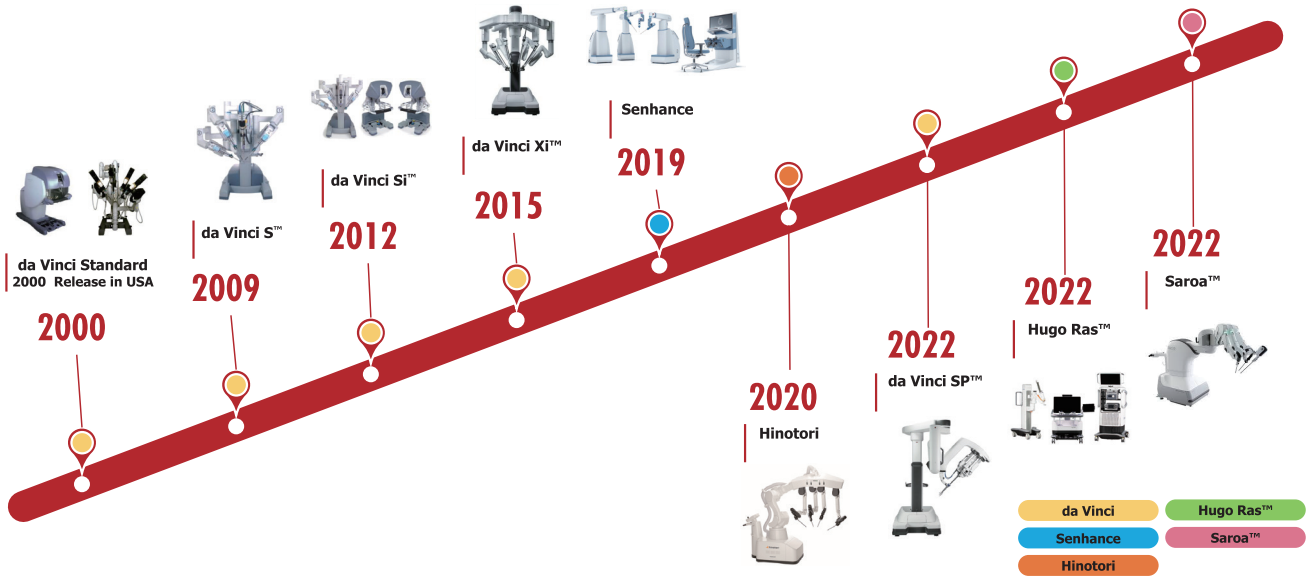

Figure 1 Time line of robotic surgical systems in Japan

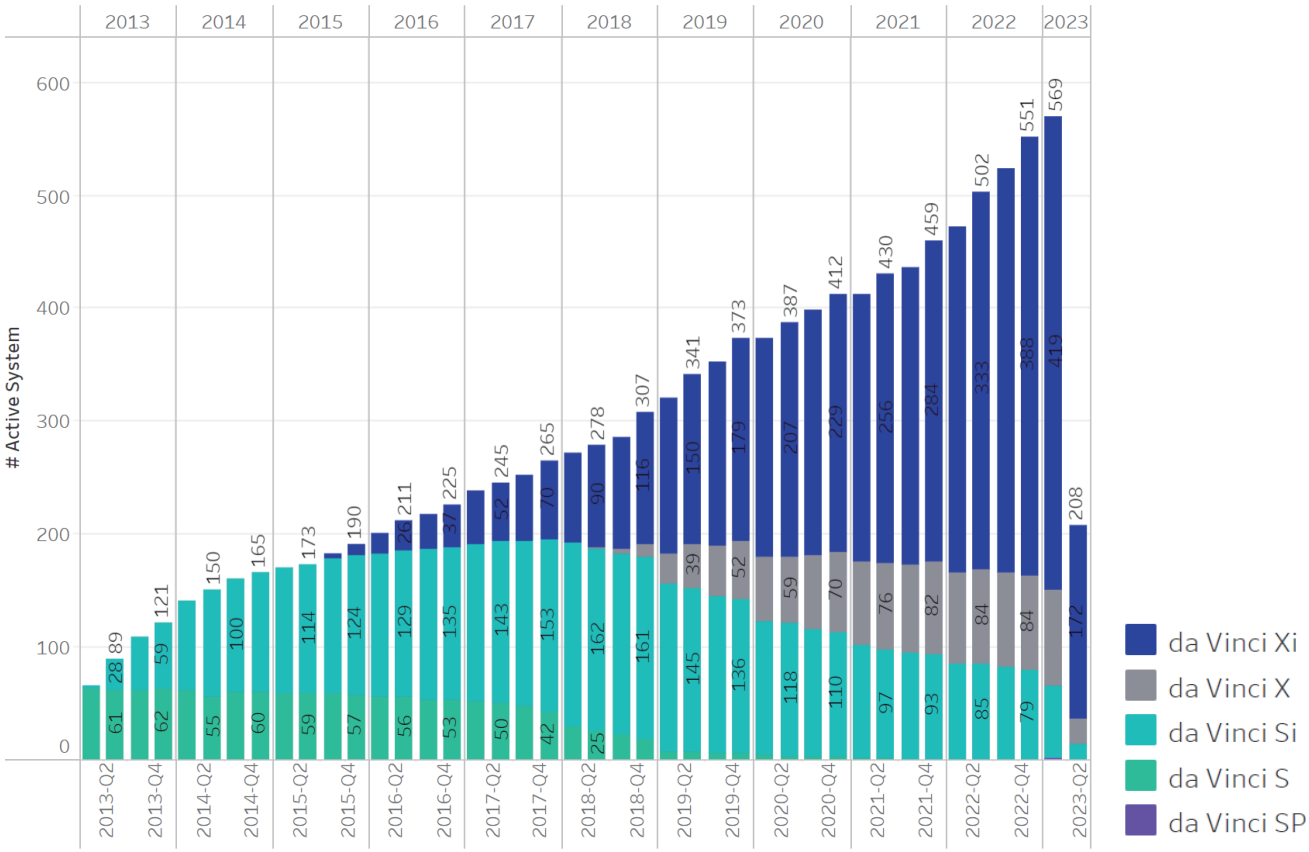

Figure 2 Number of da Vinci in Japan, provided by Intuitive Surgical Inc.

remain a barrier for many hospitals[11].

Japan's first robot-assisted surgery device, the "Hinotori Surgical Robot System," developed by Medicaroid Corporation, was approved for manufacture and sale by the Ministry of Health, Labor and Welfare in August 2020, with insurance coverage following in September of the same year. The Hinotori system features a compactly designed surgical arm with eight axes, surpassing the seven axes of the preceding da Vinci system. This design minimizes arm-to-arm and arm-to-assistant interference, enabling smoother surgical operations. Robot-

ic-assisted laparoscopic total prostatectomies using the Hinotori system have shown promising results[12]. Currently, Hinotori is also utilized in surgeries within the surgical and gynecological fields[13–15]. The author has performed robot-assisted laparoscopic radical prostatectomies using Hinotori. During the transition from the da Vinci to the Hinotori system, initial discomfort was noted in the docking system and forceps operation. However, these issues were resolved with each successive case. Additionally, research is underway in Japan to develop a teleoperative environment leveraging high-speed communication, AI, and other technologies[16–18]. The Hinotori is considered an essential system in modern medicine, significantly improving the quality of surgeries with its precise operability, 3D visualization capabilities, reduction of surgeon fatigue, flexible approach, contributions to education and training, enhancement of patient comfort, potential for remote surgery, and possibilities for continuous technological innovation. These ongoing advancements are improving surgical outcomes. In the future, the integration with AI and the introduction of new sensing technologies, in addition to remote surgery, may enable even more advanced surgical assistance. Since 2020, the number of surgeries performed with the Hinotori has increased in urology as well as in gynecology and gastroenterological surgery. By 2023, it has been introduced in 44 facilities in Japan, conducting over 3,200 surgical cases (Figure 3).

The Senhance robotic system (Asensus Surgical, Durham, NC, USA), first introduced in 2012 as TELELAP Alf-X, received European approval in 2014[19]. In Japan, Senhance gained approval from pharmaceutical affairs bodies and was included in insurance coverage in 2019. There are nine reports documenting the use of Senhance in Japanese surgical fields. The system's forceps movement is computer-controlled, with a stabilization mechanism to minimize tip blurring. The forceps tip movement is adjustable, featuring a 'tactile feedback system' that simulates direct hand control. Additionally, a 3D high-definition camera can be operated using only eye movements[20–22].

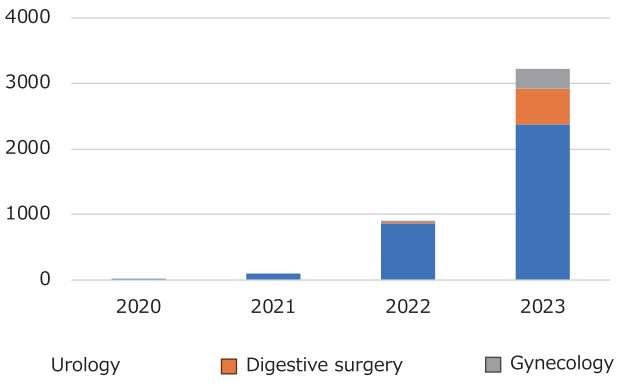

Figure 3 Hinotori cumulative number of cases, provided by Medicaroid

The Hugo Ras system developed by Medtronic and launched in Japan in December 2022, features independently positionable arms and an open console, facilitating communication with operating room staff. This system allows multiple observers to simultaneously view the surgeon's operating screen. As of now, there is no report of Hugo being used in urology in Japan, with only one report in obstetrics and gynecology[23].

Ligasure is a device developed by Covidien (which has now been acquired by Medtronic) for sealing and cutting tissues. It is widely used in conventional laparoscopic surgery because it utilizes high-frequency energy to seal tissues and cut while minimizing bleeding. Its excellent sealing capability effectively reduces bleeding during surgery and shortens recovery time post-operation. When the Hugo RAS system is now developing in combination with Ligasure, it is expected to further enhance the precision and efficiency of robotic-assisted surgeries. The integration of Ligasure could become a notably distinct feature in surgeries using the Hugo RAS, potentially offering advantages over other robotic surgery systems. Specifically, the use of Ligasure may allow for more effective control of bleeding, improve the safety of the surgery, and reduce the duration of the procedure.

The Saroa Surgical System, equipped with a 'tactile' sensation, received manufacturing and marketing approval in May 2023. Developed by Riverfield, a venture originating from Tokyo Institute of Technology and Tokyo Medical and Dental University, Saroa stands out for its pneumatically movable arms and pressure sensors that convey force directly to the doctor's fingertips. Conventional surgical support robots rely solely on visual information obtained from camera images, but Saroa has the ability to estimate the forceps' grasping force from control information and feed it back to the controller operated by the doctor. This allows

the physician operating the robot to perform the procedure as if he or she were operating directly with his or her own hands, and is expected to realize safer and more precise surgery[24, 25]. The Saroa system's patient cart and surgeon's console are about half the weight of traditional systems, offering ease of movement within facilities. The surgeon's console, similar to the Hugo RAS system, is an open platform. Although robotic surgeries using Saroa have commenced in the field of urology, no literature reports are available yet[26].

To enhance the safety of robotic surgery for each model, the Japanese Society of Endourology and Robotics and the Japan Society for Endoscopic Surgery etc. have established training systems, certification methods, and proctoring systems for performing robotic surgery on more than one model. These systems refer to education and training specialized for specific robotic surgery systems (for example, the da Vinci surgical system or other competing robotic systems). These training programs are designed to enable surgeons to learn how to use a specific robotic surgery system and to maximize their surgical skills within that system.

Comparison of various robotic systems in urological surgery

In the field of urology, robotic-assisted laparoscopic surgery, characterized by magnified high-resolution 3D imaging, a wide range of motion in forceps joints, and significant operational freedom, is applicable for a variety of conditions. These include adrenal tumors, renal cell carcinoma, renal pelvis and ureter cancer, prostate cancer, bladder cancer, congenital hydronephrosis, and pelvic organ prolapse. When compared to open surgery and traditional laparoscopy, robotic-assisted laparoscopic surgery offers several advantages, such as reduced blood loss, improved perioperative outcomes, better functional preservation, shorter hospital stays, and enhanced quality of life. However, it also presents certain disadvantages:

- High operational costs, including maintenance and management expenses.
- In Japan, insurance reimbursement rates are low (no additional points for robotic usage).
- Significant non-reimbursable costs for materials.
- Lack of compatibility between the da Vinci system and other models in terms of cameras and surgical equipment.
- Complex requirements for surgical accreditation as stipulated by professional societies.

Although each new surgical robotic system is designed to address the technical or cost limitations of the da Vinci platform, a comparison of these surgical robots was conducted from the perspectives of setup, ease of use, device options, medical costs, surgical education, and teleoperation capabilities (Table 1). In terms of forceps variety, the da Vinci system is superior with thirty-nine types and also supports the use of sealing devices and automated anastomosis devices. Haptic feedback, a feature that simulates the sense of touch, is available with both the Senhance and Saroa systems. The console types of Senhance, Hugo Ras, and Saroa are open, which facilitates easier communication with the surgical assistant. A study comparing the Hugo Ras and da Vinci systems in robot-assisted laparoscopic radical prostatectomies reported no significant differences in total operative time or console time. However, it was noted that docking took longer with the Hugo Ras, which was attributed to its initial introduction phase[27]. In robot-assisted laparoscopic partial nephrectomy (RAPN), Miyake

Table 1 Comparison of robotic surgical systems in Japan

	Da Vinci (Xi)	Hinotori	Senhance	Hugo Ras	Saroa
Types of forceps	39	11	42	8	6
Haptic feedback	×	×	○	×	○
Simulator	○	○	○	○	×
Teleoperation capability	×	Under development	×	×	Under development
Consol type	Close	Close	Open	Open	Open
Cost of unit (List Price: million yen)	275	235	200	230	Open price

As of January 4, 2024

et al. reported their surgical experience with 30 cases using the Hinotori system, achieving good results despite a short follow-up period. Additionally, a study comparing perioperative outcomes of RAPN using Hinotori and da Vinci was conducted. This analysis used propensity score matching and included 303 patients who underwent RAPN with da Vinci and 40 patients who underwent the procedure with Hinotori. The study found no significant differences in primary perioperative outcomes between the two systems, including operative time, robotic system use time, and warm ischemia time. The achievement of 'trifecta' has been proposed as a comprehensive surgical outcome measure for partial nephrectomy. It evaluates whether the surgery meets all of the following goals: effective cancer control, preservation of renal function, and avoidance of complications[28]. There were no significant differences in the rates of achieving trifecta, transection positivity, ischemia, and complication outcomes between the two groups. Additionally, changes in estimated glomerular filtration rate at 1 and 28 days post- RAPN were similar for both groups[29]. This surgical robot Hinotori has several features that differentiate it from existing systems, including: software calibration of the trocar position without the need to attach the trocar, a compact operation arm with 8 axes of motion, and a flexibly positioned 3D viewer in the surgeon's cockpit. These advantages of hinotori are expected to reduce interference between the arms and between the arms and the doctor in a clean field, allowing the surgery to proceed smoothly. Importantly, the surgeon's cockpit reduces the burden on the surgeon with its ergonomic design. In Japan, various robotic systems are available for procedures such as robotic-assisted laparoscopic nephrectomy[30], robotic-assisted laparoscopic total bladder cystectomy, and robotic-assisted laparoscopic adrenalectomy[31]. Further evaluation of each system's efficacy in these specific techniques is anticipated.

Education of robotic surgery

Currently, most localized malignancies, with the exception of advanced cancers, can be treated using laparoscopic surgery. Surgeons, including urologists, are required to acquire safe and well-established techniques for robot-assisted laparoscopic surgery. The learning curve for robotic surgery techniques has been reported to be comparable in duration to that of traditional laparoscopic surgery, where forceps are manually handled, especially in the context of robotic-assisted laparoscopic total prostatectomy[32]. In the past, the initial step in learning laparoscopic surgery involved studying surgical videos and practicing in a dry box. In the realm of robotic surgical education, in addition to video learning, training can also be conducted using a simulation image system on the console (Table 1). Various robotic platforms applied in surgery include the Revo-i Robotic Surgical System (Meere Company Inc., Seongnam, Republic of Korea), Avatera (avateramedical GmbH, Jena, Germany), and the Versius Surgical System (CMR Surgical, Cambridge, UK). As these technologies evolve, the global robotic surgical equipment market is expected to become increasingly competitive in the future[11]. A crucial question now is what educational steps and systems will be implemented to train young surgeons who have limited experience in open and laparoscopic surgery.

Future direction of robotic surgery

The integration of AI and robotic surgery represents a significant advancement in medical technology of urology field[33]. Here are the key aspects of how AI and robotic surgery are working together. AI utilizes image analysis technologies to extract detailed information from medical images such as MRI, CT scans, and X-rays. This enhances the accuracy of diagnostics in the preoperative planning phase, thereby enhancing the precision of surgeries. Additionally, AI algorithms can analyze patient-specific data to determine the most suitable surgical approach, enabling the creation of customized surgical plans for each patient and minimizing risks. Robotic surgical systems use data provided by AI to perform more accurate and precise movements during surgery, allowing surgeons to operate with high precision in tight areas or on minute tissues. During surgery, AI can analyze data in real-time, providing critical information to surgeons and enabling more informed decision-making, thus improving the safety and efficacy of the surgery. Furthermore, AI systems can learn from past surgical data to provide insights for improving the success rates of future surgeries[34-36].

This promises advancements in surgical tech-

niques and better patient outcomes. Even in the post-operative period, AI can monitor patient recovery and recommend necessary interventions, enhancing the overall quality of care. Future directions for robotic surgery training may include the use of technologies such as AI and machine learning for real-time feedback, remote mentoring, and augmented reality platforms, aiming to reduce costs and overcome geographic limitations[37].

In current robot-assisted surgical approaches, surgeons mainly operate rigid, metallic robotic devices, resulting in limited operability. Soft Robotics, characterized by the use of flexible materials like silicone, rubber, and plastic, allows operation in complex shapes and convoluted environments. This field aims to emulate biological flexibility and adaptability, achieving more natural and flexible movements compared to traditional robotic designs that use metal for both the robot's links and joints. This enables changes in shape and rigidity that were previously impossible. If control issues can be resolved, soft robotics could become central to the next generation of robotic surgery[38, 39]. Its flexible structure offers greater safety in interactions with humans and the environment, making it suitable for medical applications and collaborative work. Soft robots are expected to adapt and deform in response to their environment, akin to biological muscles. In the medical field, these characteristics enable flexible surgical robots to operate in narrow spaces and perform precise tasks challenging for traditional rigid robots. Soft robotics is a nascent field with challenges like durability, precise control of force, programming complex movements, and improving energy efficiency[40].

In the future, soft robotics has the potential to transform the role of robots in many medical fields by achieving more natural and human-like movements and improving interactions with humans, especially when combined with advanced AI. This innovative field brings a new dimension to robot technology with its flexibility, safety, and adaptability, potentially enabling a future where robots are deeply integrated into human life. Despite the technical challenges, advancements in this medical field are expected to push the boundaries of robotics, promoting the development of more flexible and interactive robots (Figure 4).

Conclusion

Twenty-four years have elapsed since the introduction of the da Vinci robotic surgery system in Japan. Several areas in the robotic surgery platform, including newer models, require improvements. These improvements include enhancing communication with assistants through open consoles, improving modularity, ensuring compatibility with other models, reducing equipment size, and lowering costs. Additionally, the insurance system in Japan presents barriers to robotic surgery,

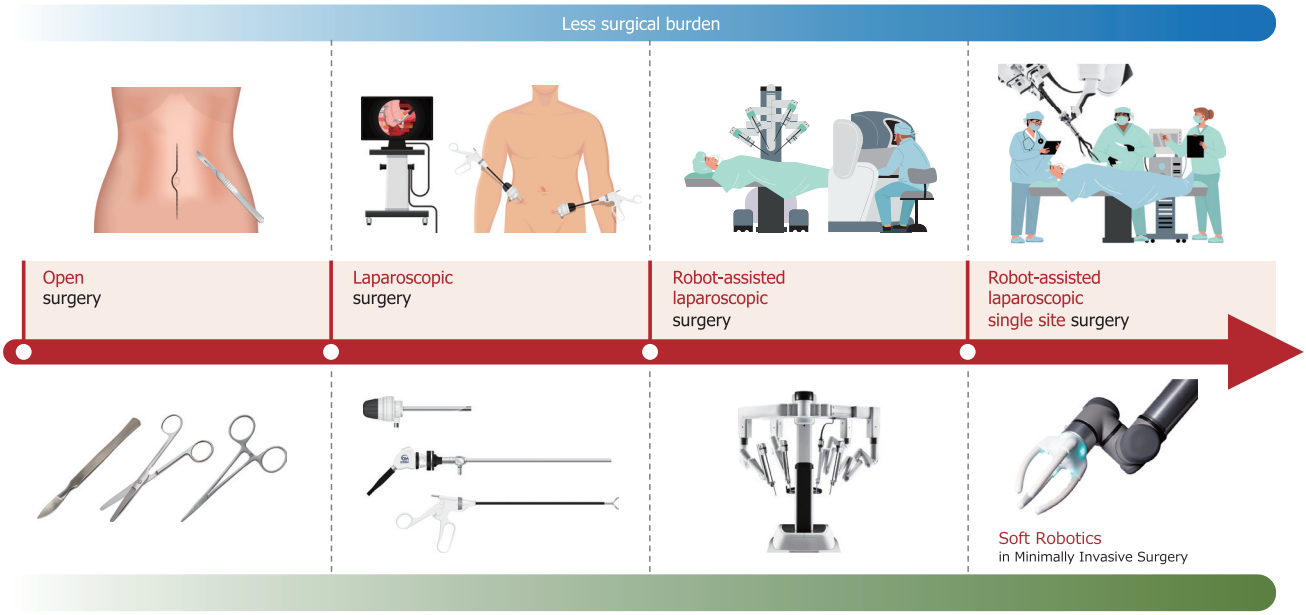

Figure 4 Evolution of robotics in minimally invasive surgery

such as low reimbursement rates for robotic procedures, the absence of additional fees for robotic surgery depending on the procedure, high costs of non-reimbursable materials, and the complexity of surgical accreditation requirements set by academic societies. As robotic surgery continues to mature clinically and as technology evolves, we can anticipate the development of new systems that incorporate artificial intelligence technology in various surgical fields.

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Author contributions

HI planned this manuscript, collected the appropriate literature information, and drafted the manuscript. The author read and approved the final manuscript.

Conflicts of interest statement

The author declares that there are no conflicts of interest.

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Reviews

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Neurosteroid Binding and Actions on $GABA_A$ Receptors

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Neurosteroids positively modulate $GABA_A$ receptor ($GABA_AR$) channel activity by binding to a transmembrane domain intersubunit site. Using photo-affinity labeling and an ELIC-α_1GABA_AR chimera, we investigated the impact of mutations within the intersubunit site on neurosteroid binding. These mutations reduce neither photolabeling within the intersubunit site nor competitive prevention of labeling by allopregnanolone. Instead, these mutations change the orientation of neurosteroid photolabeling. The data indicate that mutations at Gln242 or Trp246 that eliminate neurosteroid effects do not eliminate neurosteroid binding within the intersubunit site, but significantly alter the preferred orientation of the neurosteroid within the site. The interactions formed by Gln242 and Trp246 within this pocket play a vital role in determining the orientation of the neurosteroid. We also examined how site-specific binding to three identified neurosteroid-binding sites in the $\alpha_1\beta_3GABA_AR$ contributes to neurosteroid allosteric modulation. We found that the potentiating neurosteroid, allopregnanolone, but not its inhibitory 3β-epimer epi-allopregnanolone, binds to the canonical $\beta_3(+)$-$\alpha_1(-)$ intersubunit site that mediates receptor activation by neurosteroids. In contrast, both allopregnanolone and epi-allopregnanolone bind to intrasubunit sites in the β_3 subunit, promoting receptor desensitization and the α_1 subunit promoting effects that vary between neurosteroids. Two neurosteroid analogues with diazirine moieties replacing the 3-hydroxyl bind to all three sites, but do not potentiate $GABA_AR$ currents. One is a desensitizing agent, whereas the other is devoid of allosteric activity. Collectively, these data show that differential occupancy and efficacy at three discrete neurosteroid-binding sites determine whether a neurosteroid has potentiating, inhibitory, or competitive antagonist activity on $GABA_AR$.

Key words: neurosteroid, GABA-A receptor, photo-affinity labeling, electrophysiology, binding site

Steroid hormones can cross the blood-brain barrier and function at the genomic level to produce changes in mood and behavior. These effects develop relatively slowly over minutes to hours, and can persist long after the disappearance of the steroid from the brain. However, certain steroids can produce immediate changes within seconds in neuronal excitability on a timescale that precludes a genomic locus of action.

What are neurosteroids and where are they made?

The central depressant action of cholesterol was first reported more than three-quarters of a century ago. Subsequently, in the 1940s, it was shown that certain pregnane steroids was able to induce rapid sedation and anesthesia. The steroid structure (Figure 1) contains the chiral centers at C3, C5 and C17 and 3α-hydroxypregnane steroids have been suggested to potentiate γ-aminobutyric acid type A receptors ($GABA_AR$).

Steroids were thought to act exclusively as hormones and to originate from endocrine glands, such as the ovaries and adrenal glands, so they would need to cross the blood-brain barrier before they could influence neuronal signaling. However, the brain is also a steroidogenic organ. Certain

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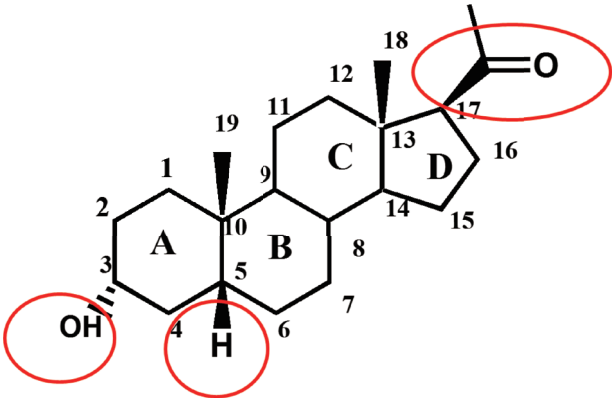

Figure 1 Steroid structure
Structure of neurosteroid with carbon atoms numbered and steroid rings labeled. Red circles emphasize the chiral centers at C3, C5 and C17.

neurons and glia in the central nervous system express the enzymes that are required for the local synthesis of pregnane neurosteroids (NS)[1].

What do endogenous neurosteroids do?

GABA is released from vesicles rapidly activates a family of postsynaptic $GABA_AR$, which gives rise to inhibitory postsynaptic current. NS that are released locally from neurons or glia prolong the decay of such responses, enhancing synaptic inhibition. In addition, certain neurons contain extrasynaptically-located receptors that are activated by low levels of ambient GABA to cause a 'tonic' inhibition. Some NS appear to engage other targets, such as NMDA receptors, T-type calcium channels and toll-like receptors[2].

How do neurosteroids work?

In the early 1980s, Harrison and Simmonds showed that certain endogenous steroids are potent positive allosteric modulators of the $GABA_AR$[3]. Subsequent studies also showed potent stereo-selective GABA-modulatory effect of NS.

The $GABA_AR$ are pentameric ligand-gated ion channels that include other receptors such as acetylcholine receptors, glycine receptors and serotonin receptors. Transmembrane domains of $GABA_AR$ are one of main targets of anesthetic action. NS are thought to potentiate the $GABA_AR$ by direct interactions at specific sites within the transmembrane domains. The second part of four transmembrane domains from each subunit construct an ion channel pore of the $GABA_AR$. Recent photoaffinity labeling and crystallographic studies have shown that NS bind to a specific site between adjacent subunits that mediates $GABA_AR$ potentiation[4-8].

Identifying neurosteroid anesthetic binding sites

My research focuses on identifying NS anesthetic binding sites on membrane proteins by means of photo-affinity labeling, mass spectrometry and cryogenic electron microscopy. Photoaffinity labeling is a rapid and inexpensive method. It can be performed in cells or native membranes. However, there are a few limitations of photo-ligands in terms of specificity, efficiency, and non-identity to anesthetic. Lack of 3-D structure is also a limitation of photoaffinity labeling. The principle of photolabeling is that a NS photolabeling reagent covalently attaches to a binding site with UV irradiation (Figure 2). Mass spectrometric analysis on photolabeled membrane protein can localize binding sites, stoichiometry and photolabeling efficiency.

With this novel approach, we have identified NS binding sites in $GABA_AR$ transmembrane domains. One is between β_3 and α_1 subunits, others locate within a β_3 or α_1 subunit. We call them as inter-subunit binding site and intra-subunit binding site, respectively. We have shown that both inter- and α_1 intra-subunit sites contribute to NS potentiation of $GABA_AR$ by electrophysiological experiments and site-directed mutagenesis[7].

Neurosteroid hydrogen bonding drives binding orientation

Within the intersubunit site, two key residues, Gln242 and Trp246, are shown to form hydrogen bond and hydrophobic ring-stacking interactions, respectively, with the NS. To date, functional studies have demonstrated that mutations of the two key residues abolish the NS potentiating effect (Figure 3). Based on these findings, it was suggested that these mutations abolish potentiation by reducing or eliminating NS binding. There was, however, no experimental evidence to evaluate whether these mutations alter NS binding or affect transduction of the binding signal. We therefore tested the effect of mutations on the efficiency, stoichiometry and sites of NS photolabeling in order to evaluate whether these mutations reduce NS binding, change binding orientation or affect transduction of the

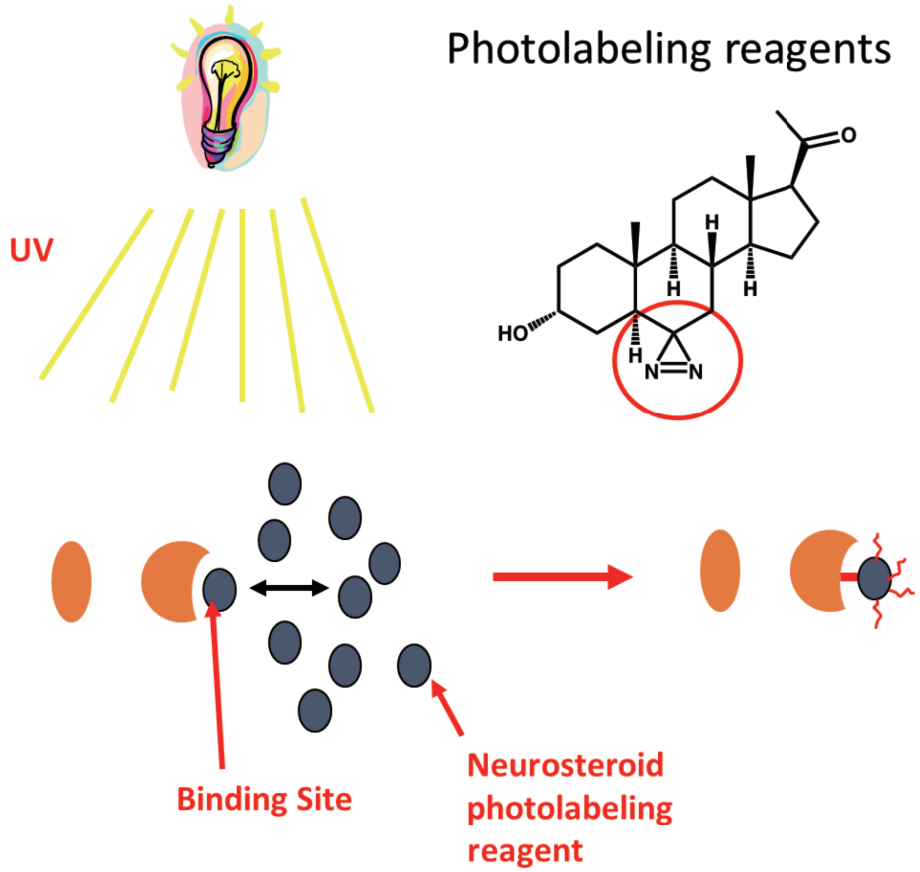

Figure 2 Principle of photolabeling
A neurosteroid photolabeling reagent covalently attaches to a binding site with UV irradiation.

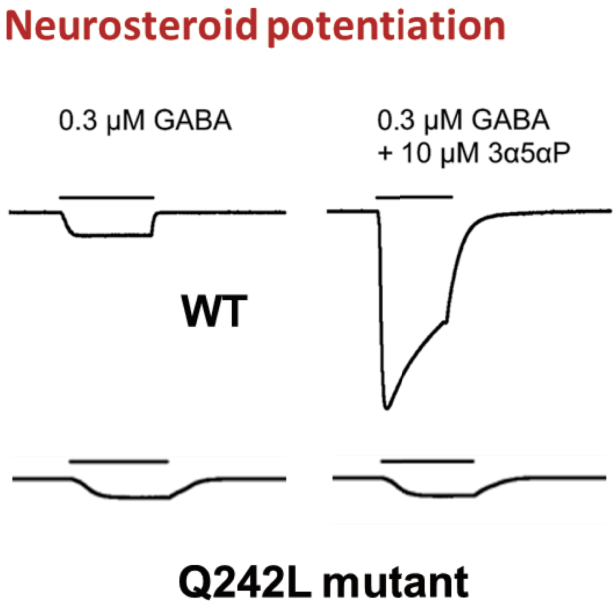

Figure 3 Neurosteroid potentiation
Sample current traces from $\alpha_1\beta_3$ $GABA_AR$ WT activated by 0.3 μM GABA showing potentiation by 10 μM 3α5αP and the absence of potentiation by 10 μM 3α5αP in the mutant, α_1(Q242L)β_3 $GABA_AR$ activated by 0.3 μM GABA.

binding signal. To enable the use of mass spectrometric analysis of photolabeled $GABA_AR$ transmembrane domains and the expression of multiple mutants, we expressed an ELIC-α_1GABA_AR chimera.

Our NS photolabeling reagents labeled the ELIC-α_1GABA_AR chimera with stoichiometry of two using two established allopregnanolone (3α5αP)-based photolabeling reagents, KK123 and KK200. The primary aim of this study is to test whether the loss of these functionally important interactions disrupt NS binding. To address this, we photolabeled ELIC-α_1GABA_AR chimera mutants with KK200. Analysis of the labeled mutants by intact protein mass spectrometry showed labeling efficiencies identical to WT, suggesting that NS still bind to mutant ELIC-α_1GABA_AR. This finding contradicts the idea that these mutations disrupt NS binding. To confirm that the endogenous NS, 3α5αP, also binds to the intersubunit site of the Q242W or W246L mutant transmembrane domains, we tested whether 100 μM 3α5αP competitively

reduces the labeling efficiency of 10 μM KK200 in WT, Q242W and W246L mutants. Indeed, 3α5αP reduced the photolabeling efficiency of KK200 for the intersubunit site to the same extent in WT and both mutants suggesting that 3α5αP binds to the intersubunit site in both WT and the mutants.

Next, we used a middle-down mass spectrometric analysis to identify the residues labeled by KK200 in each mutant. Just as in WT, KK200 labeled the same Asn408 in the intrasubunit site in all three mutants. Surprisingly, unlike WT, where KK200 labeled Tyr309 in TM3 which forms the intracellular end of the intersubunit pocket, KK200 labeled Phe298 in the mutants. Thus, KK200 photolabeling of Phe298 in all three mutants, instead of Tyr309, indicates that Gln242 and Trp246 are important determinants of NS binding orientation.

It is possible that the changes in photolabeling observed for KK200 are not reflective of binding for the endogenous NS, 3α5αP. To address this possibility, we examined computational docking of 3α5αP to the WT and Q242W α_1GABA_AR transmembrane domains. The respective binding modes of the docking results are consistent with KK200 labeling of Tyr309 in WT and Phe298 in the Q242W mutant. Collectively, the data indicate that mutations at Gln242 or Trp246 that eliminate NS effects do not eliminate NS binding within the intersubunit site, but significantly alter the preferred orientation of the NS within the site[8].

Inter- and α_1 intra-subunit sites contribute to neurosteroid potentiation of $GABA_A$ receptors

Our recent photo-labeling studies have confirmed that there are multiple positive allosteric modulatory (PAM)-NS-binding sites on $\alpha_1\beta_3$ $GABA_AR$[7]. In addition to the site at the interface between the transmembrane domains of adjacent subunits which is called an intersubunit site, we identified NS binding sites within the α-helical bundles of both the α_1 and β_3 subunits of $\alpha_1\beta_3$ $GABA_AR$. 3α5αP binds to all three sites, and mutagenesis of these sites suggests that the intersubunit and α_1 intrasubunit sites, but not the β_3 intrasubunit site, contribute to PAM activity of 3α5αP. A functional effect for NS binding to the β_3 intrasubunit site had not been identified.

Dissociation of neurosteroid $GABA_A$ receptor activation and enhancement of orthosteric ligand binding

We hypothesized that various NS analogues preferentially bind to one or more of the three NS binding sites in the $\alpha_1\beta_3$ $GABA_AR$, stabilizing distinct conformational states (i.e. resting, open or desensitized). To achieve this goal, we used two endogenous NS, the PAM-NS 3α5αP and the negative allosteric modulatory (NAM)-NS epi-allopregnanolone (3β5αP) and two NS analogues, KK148 and KK150, in which a diazirine replaced the function-critical 3-OH group. We examined site-specific NS binding and effects using photolabeling and measurements of channel gating and orthosteric ligand binding. The NS lacking a 3α-OH were devoid of PAM activity, but surprisingly, KK148 and 3β5αP enhanced the affinity of orthosteric ligand, [^{3}H]muscimol binding. We interpret this finding as evidence that these compounds preferentially bind to and stabilize desensitized receptors, since both open and desensitized $GABA_AR$ exhibit enhanced orthosteric ligand-binding affinity[9].

Effects of neurosteroids on desensitization of $GABA_A$ receptor

Many 3β-OH NS are $GABA_AR$ NAM[10]. Co-application of 3β5αP with 1 mM GABA preferentially inhibited steady-state rather than peak currents. The inhibitory effect of 3β5αP was not observed in receptors with the α_1(V256S) TM2 pore-lining mutation, which was previously shown to remove the inhibitory effects of steroids[10, 11]. To examine the inhibitory effect of the NS analogues, we activated $\alpha_1\beta_3$ $GABA_AR$ with a saturating concentration of GABA and tested the effect of the NS on steady-state currents. KK148 and 3β5αP both decreased steady-state currents, whereas KK150 did not.

Which sites do neurosteroid analogues bind?

To determine whether KK148 and 3β5αP stabilize a desensitized conformation of the $GABA_AR$ by selectively binding to one or more of the identified NS binding sites on the $GABA_AR$, we first determined which of the identified NS-sites they bind. We have previously shown that the 3α5αP-analogue photolabeling reagent, KK200 labels the β_3(+)-α_1(-) intersubunit and a α_1 intrasubunit sites

on $\alpha_1\beta_3$ $GABA_AR$, and that photolabeling can be prevented by a 10-fold excess of 3α5αP. As a first step to determine the binding sites for 3β5αP, KK148 or KK150, we examined whether a 10-fold excess of these compounds (30 mM) prevented KK200 (3 mM) photolabeling of either binding site.

KK148, KK150, 3α5αP and 3β5αP all prevented KK200 photolabeling of α_1Asn408 in the α_1 intrasubunit site, consistent with their binding to this site. In contrast, KK148, KK150 and 3α5αP but not 3β5αP prevented labeling of the intersubunit site, indicating that 3β5αP does not bind to the intersubunit site.

The KK148- and KK150-photolabeled samples were also analyzed to directly identify the sites of adduction. In both the KK148- and KK150-labeled samples, photolabeled peptides were identified from the TM4 helices of both the α_1 and β_3 subunits.

We have also shown that KK123 labeling of the α_1 intrasubunit (α_1Tyr415) and β_3 intrasubunit (β_3Tyr442) sites can be prevented by a 10-fold excess of 3α5αP. Thus, we examined whether 3β5αP inhibited photolabeling by KK123. 3β5αP completely inhibited KK123 photolabeling at both intrasubunit sites.

Collectively, the data show that KK148, KK150 and 3α5αP bind to all three of the identified NS binding sites. In contrast, 3β5αP selectively binds to the two intrasubunit binding sites, but not to the $\beta_3(+)$–$\alpha_1(-)$ intersubunit site[12].

Sites of neurosteroid action on [^{3}H]muscimol binding

To determine which of the previously identified binding sites contributes to NS enhancement of [^{3}H]muscimol binding, we performed site-directed mutagenesis of the NS-binding sites previously determined by photolabeling. Specifically, α_1(Q242L)β_3 targets the $\beta_3(+)$–$\alpha_1(-)$ intersubunit site, α_1(N408A/Y411F)β_3 and α_1(V227W)β_3 the α_1 intrasubunit site, and $\alpha_1\beta_3$(Y284F) the β_3 intrasubunit site.

Mutations in the $\beta_3(+)$–$\alpha_1(-)$ intersubunit and α_1 intrasubunit sites decreased 3α5αP enhancement of [^{3}H]muscimol binding by ~80%, while mutation of the β_3 intrasubunit site led to a small decrease. The residual enhancement of [^{3}H]muscimol binding observed in receptors with mutations in the intersubunit or α_1 intrasubunit site occurs at 10-fold higher concentrations of 3α5αP than WT and receptors with mutations in the β_3 intrasubunit site, suggesting that 3α5αP binds to the β_3 intrasubunit site with lower affinity. In contrast, mutations in the α_1 and β_3 intrasubunit sites, but not the intersubunit site decreased the enhancement of [$_3$H]muscimol binding by 3β5αP and KK148.

Collectively, these results show that multiple NS binding sites contribute to enhancement of [^{3}H]muscimol affinity and that potentiating NS (3α5αP) and non-potentiating NS (3β5αP, KK148 and KK150) have both common and distinct sites of action[12].

Sites of 3β5αP desensitization of $GABA_A$ receptor

To further explore the relationship between desensitization and enhancement of [^{3}H]muscimol binding, we examined the consequences of mutations to these sites on physiological measurements of desensitization induced by NS. 3β5αP reduced the steady-state current by 23.0%. Mutations in the α_1 and β_3 intrasubunit sites prevented 3β5αP-enhanced desensitization by ~67%, whereas mutation in the $\beta_3(+)$–$\alpha_1(-)$ intersubunit site was without effect. Receptors with mutations in both the α_1 and β_3 intrasubunit sites showed less NS-enhancement of desensitization than receptors with mutations in either of the intrasubunit sites alone, indicating that both intrasubunit sites contribute to the desensitizing effect. Since mutations of the α_1 and β_3 intrasubunit sites also disrupt 3β5αP-enhancement of [^{3}H]muscimol binding, we conclude that 3β5αP binding to these intrasubunit sites stabilizes the desensitized state of the $GABA_AR$ and enhances [^{3}H]muscimol binding.

Sites of 3α5αP desensitization of $GABA_A$ receptor

3α5αP binds to all three of the neurosteroid binding sites on $\alpha_1\beta_3$ $GABA_AR$, and mutations in all three sites reduce 3α5αP enhancement of [^{3}H]muscimol binding. This suggests the possibility that activation by 3α5αP (mediated primarily by the $\beta_3(+)$–$\alpha_1(-)$ intersubunit site) masks a desensitizing effect mediated through the β_3 and/or α_1 intrasubunit binding sites. To determine whether intrasubunit binding sites mediate increased desensitization by 3α5αP, we examined the effect of 3α5αP on steady-state currents in receptors with mutations in the α_1 or β_3 intrasubunit site. Mutations in the intrasubunit sites were prepared with

a background α_1(Q242L)β_3 mutation to remove 3α5αP activation and focus on the effects of 3α5αP on the equilibrium between the open and desensitized states. 3α5αP produced a small reduction in steady-state current in α_1(Q242L)β_3 receptors with mutations in neither of the intrasubunit sites. This inhibitory effect was eliminated by α_1(V256S)β_3, indicating that it was due to receptor desensitization. In receptors with combined mutations in the intersubunit and α1 intrasubunit sites, 3α5αP significantly inhibited the steady-state current, an effect that was markedly reduced by mutations in the β_3 intrasubunit site. These data suggest that 3α5αP exerts a desensitizing effect by binding to the β_3 intrasubunit site and that 3α5αP binding to the α_1 intrasubunit site does not promote desensitization.

Conclusion

Here, we examined how site-specific binding to the three identified neurosteroid sites on $\alpha_1\beta_3$ $GABA_AR$ contributes to the PAM vs. NAM activity of epimeric 3-OH NS. We found that the PAM-NS 3α5αP, but not the NAM-NS 3β5αP, binds to the canonical β_3(+)–α_1(−) intersubunit site that mediates receptor potentiation, explaining the absence of 3β5αP PAM activity. In contrast, 3β5αP binds to intrasubunit sites in the α_1 and β_3 subunits, promoting receptor desensitization. Two synthetic NS with diazirine moieties at C3 (KK148 and KK150) were used to identify NS binding sites and shown to bind to the intersubunit as well as both intrasubunit sites. KK148 is an efficacious desensitizing agent, acting through the α_1 and β_3 intrasubunit NS binding sites. KK150, the 17α-epimer of KK148, binds to all three NS binding sites, but neither activates nor desensitizes $GABA_AR$, suggesting a potential chemical scaffold for a general NS antagonist.

Collectively, these data show that differential occupancy of and efficacy at three discrete NS binding sites determines whether a NS ligand has PAM, NAM, or potentially NS antagonist activity on $GABA_AR$.

It remains to be determined whether there are additional unique sites on γ or δ subunits or isoform specificity in neurosteroid binding within the α_{1-6} or β_{1-3} subunits. Either of these possibilities could provide specific pharmacologic targets for $GABA_AR$ subtypes.

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Author contributions

The author read and approved the final manuscript.

Conflicts of interest statement

The author declares that there is no conflict of interest.

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編集後記

2024年になってから、3件の対面式の学会大会に参加しました。どの大会でも、緊張感が漂う会場で口頭発表があり、久しぶりに活発な質疑応答がなされている風景を目にしました。また、どの学会のポスターセッションも連日盛況で、発表者と参加者がその場で質問や意見を何度も交わすことができており、多くの学会員にとって、研究に対する理解が深まり、学会参加が研究の質を向上させるよい機会になっていると実感しました。

2020年からCOVID-19（新型コロナウイルス感染症）のパンデミックによって、多くの学会がオンラインでの開催を強いられてきました。学会のオンライン開催には、いくつかメリットがありました。開催地への渡航や会場間の移動が不要のため、参加者は時間を効率的に使えました。また、シンポジウム講演や一般口頭発表では、発表スライドがPC上で音声と共に目の前に現れるため､情報を得られやすいメリットがあったと思います。一方、デメリットとしては、発表時間外に発表者と参加者が詳しく話をしたり、知り合う機会がとれない、特に新しい人と知り合うことが難しい点が挙げられたと思います。

学会大会や研究会等では、共通の関心を持つ研究者や専門家と深い交流が可能となり、新たなコラボレーションの機会が生まれやすくなります｡特に､偶然の出会いやサイドイベントを通じた非公式な交流も重要になります。ランチや情報交換会の場において、たまたま隣に座ったことで行われる雑談が、新たなアイデアやインスピレーションの源となった経験を私は持っています。私自身、予期せぬ出会いや出来事がキャリアを左右することもありました。偶然の出会いや出来事が起きたとき、その後の行動や努力で新たなアイデアやキャリアに繋がることがあると思います。何か起きるのを待つのではなく、意図的に行動できる場として、やはり学会大会は、1年に1度、当該学会員が最新のデータや知見を持ち寄り、対面式で集えるプラットホームとして機能してほしいと願います。

町田　修一
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イラスト作者より

教室のモチーフにしようと､花屋で小さなガジュマルを買ってきました。この木は沖縄で精霊（キジムナー）が宿っているといわれ縁起の良い植物だそうです。レッスン後、一回り大きな器に植え替えて室内で育ててみようと思っています。（宮道明子）

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抄　録

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神経ステロイドのGABA-A受容体結合と相互作用

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神経ステロイド(NS)はGABA-A受容体(GABA$_A$R)を介して神経系の興奮性と機能を調節する内因性物質であり，全身麻酔薬や抗うつ薬として臨床使用されている．GABA$_A$RのX線結晶構造解析や光親和性標識を用いた研究で，GABA$_A$R膜貫通ドメイン(TMD)の$\beta-\alpha$サブユニット間にNS結合部位が同定され，グルタミン残基(α_1Q242)との相互作用が，NSの結合とGABA$_A$Rのイオンチャネル活性化において重要とされてきた．光親和性標識とELIC-α_1GABA$_A$Rキメラを使用して，サブユニット間NS結合部位へのアミノ酸残基変異導入(Gln242またはTrp246の変異)の影響を調べたところ，変異導入はサブユニット間結合部位へのNS結合を阻害せず，代わりにNSの光親和性標識の方向を変化させた．この結果は，NSの効果を阻害する 結合部位への変異導入が，NSの結合自体は阻害しないが，NS結合の向きを大きく変化させ，それによりNSの効果を阻害する可能性を示している．また，興味深いことに，神経ステロイドは，$\alpha_1\beta_3$ GABA$_A$R TMDのαおよびβサブユニット内にも結合が観察されている．これらを含む$\alpha_1\beta_3$ GABA$_A$Rに同定された3つの結合部位への部位特異的NS結合が，NSのアロステリック調節にどのように寄与するかを調べた．陽性アロステリック調節作用を有するNSであるアロプレグナノロンは，$\alpha_1\beta_3$ GABA$_A$Rにおいて$\beta-\alpha$サブユニット間に結合するが，対照的に，アロプレグナノロンの3βエピマーであり陰性アロステリック調節作用を有するエピアロプレグナノロンは，この$\beta-\alpha$サブユニット間に結合しないことを発見した．一方で，アロプレグナノロンとエピアロプレグナノロンは，どちらもβ_3サブユニット内のNS結合部位に結合し，$\alpha_1\beta_3$ GABA$_A$Rの脱感作を促進し，α_1サブユニット内への結合ではそれぞれが異なる効果を示した．3カ所のNS結合部位が作用発現においてそれぞれ異なる役割を担い，さらに，NSの作用が，同時に複数のGABA$_A$R結合部位を介して発現することが証明された．

キーワード：神経ステロイド，GABA-A受容体，光親和性標識法，電気生理学，結合部位

この抄録は，順天堂醫事雑誌70巻3号，p239-244，2024掲載の『Neurosteroid Binding and Actions on GABA$_A$ Receptors』の和文抄録です．

順天堂医学会 会員の皆様

順 天 堂 医 学 会
会長　服部　信孝

順天堂医学会短期海外留学時助成金給付制度

順天堂医学会では短期海外留学時助成金給付制度を開始いたしました。

1. 要件

下記すべての要件を満たす者

(1) 順天堂大学（大学院を含む）の学生で 1 か月以上 12 か月未満の海外留学をする者
(2) 留学先の研究機関または財団などからの援助がない者
(3) 医学会の正会員として 1 年以上の経歴を有し、医学会費を完納している者

2. 申請書類

(1) 順天堂医学会短期海外留学時助成金申込書
(2) 所属長の推薦書
(3) 申請者の主な研究テーマ・研究業績
(4) 留学受け入れ機関の指導者からの推薦状

3. 助成金の給付金額

留学期間	助成金額
1 か月以上 4 か月未満	10 万円
4 か月以上 7 か月未満	20 万円
7 か月以上 12 か月未満	30 万円

4. 申請スケジュール（年 2 回）

申請期限	助成決定時期
6 月末	8 月
12 月末	2 月

5. 選考機関：順天堂医学会短期海外留学時助成金選考委員会

6. 助成後の義務

(1) 帰国後直近の順天堂医学会学術集会において研究成果の発表および、その内容を「順天堂醫事雑誌」に報告する。
(2) 帰国後は、順天堂大学またはその関連機関に原則として 3 年以上勤務する。

7. 本件の照会先

HP：https://www.juntendo.ac.jp/journal/membership/benefit_plan.html
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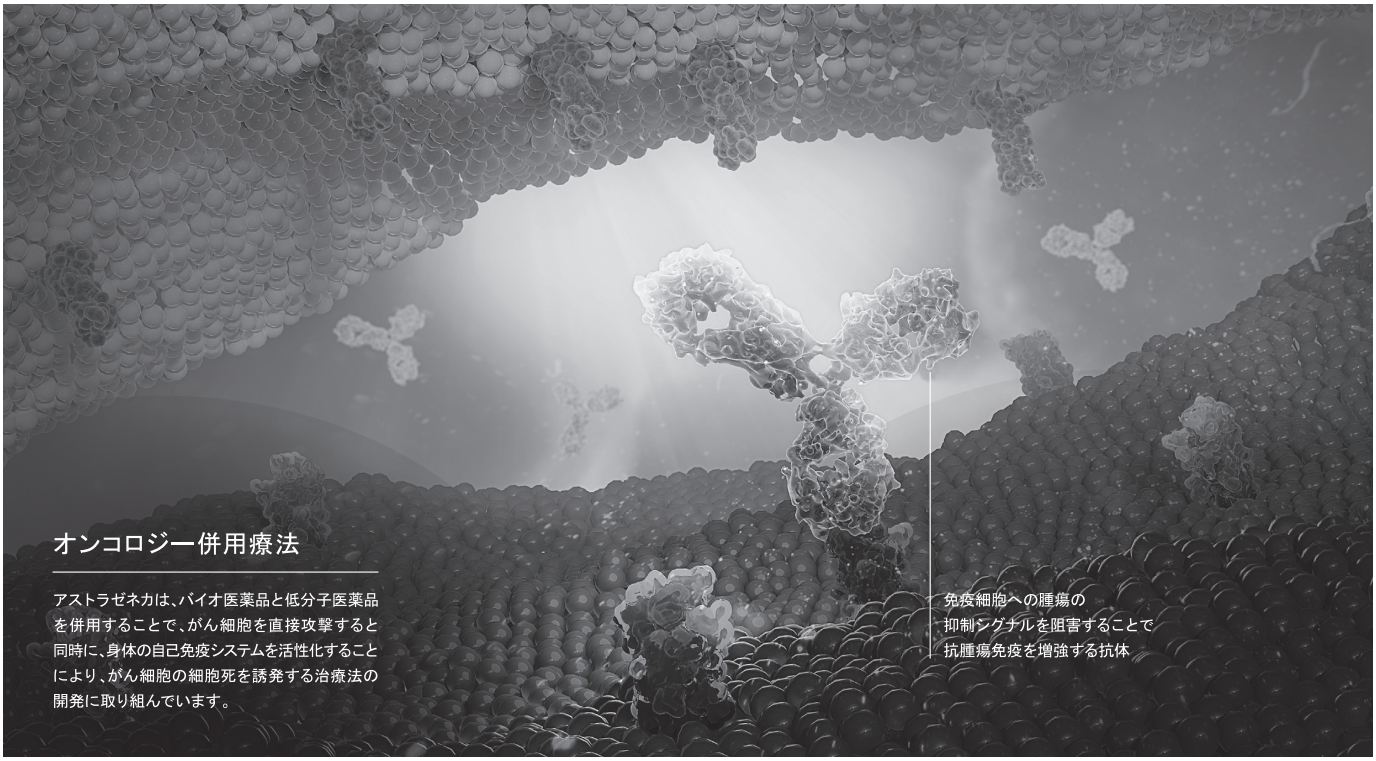

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