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REVIEW ARTICLE

Challenges and prospects of a clinical database linked to the board certification system

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Abstract In Japan, the National Clinical Database (NCD) was founded in April 2010 as the parent body of the database system linked to the board certification system. Registration began in 2011, and to date, more than 3,300 facilities have enrolled and more than one million cases are expected to enroll each year. Given the broad impact of this database initiative, considering the social implications of their activities is important. In this study, we identified and addressed issues arising from data collection and analysis, with a primary focus on providing high-quality healthcare to patients and the general public. Improvements resulting from NCD initiatives have been implemented in clinical settings throughout Japan. Clinical research using such database as well as evidence-based policy recommendations can impact businesses, the government and insurance companies. The NCD project is realistic in terms of effort and cost, and its activities are conducted lawfully and ethically with due consideration of its effects on society. Continuous evaluation on the whole system is essential. Such evaluation provides the validity of the framework of healthcare standards as well as ensures the reliability of collected data to guarantee the scientific quality in clinical databases.

Keywords Quality improvement · Database · General surgery · Cancer registry · Certification board for expert surgeons

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Introduction

When evaluating healthcare quality, it is important to consider the structure, process and outcome [1, 2]. However, Japan's healthcare policies have so far been evaluated mainly from the structural viewpoint of offering a system that provides plentiful medical care, i.e., on the number of institutions, physicians, specialists and nurses, on making sure that even a sparsely populated area has a medical facility and on ensuring that patients have access to specialists. This viewpoint of providing widespread medical care has a historical background [3]. In Japan, the fair distribution of medical resources has been politically emphasized in the context of universal health insurance. The equity of healthcare services in Japan is of international value, but when the service quality is referenced, it is important to systematically evaluate not only the structures of the services, but also their processes and outcomes.

To facilitate such evaluations, all surgical societies related to general surgery cooperated to establish the National Clinical Database (NCD), which systematically collects verified data in cooperation with various clinical fields so as to achieve the social responsibility of providing the highest quality healthcare possible in Japan [4, 5]. In order to evaluate the practices and performance of specialists, a committee for each specialty has been set up, and each of them identifies its framework for benchmarking.

As the surgical societies pay for all of the development and operating costs for the database, participating institutions can use the database system for free. Thus, it is mandatory for the institutions to participate in the benchmarking project when applying for the board certification system. Over 3,500 institutions were participating in the NCD in September 2012, and over 1,200,000 cases' data had been registered in 2011. The NCD, in cooperation with the specialist system, will provide important knowledge for future clinical database design and usage [6].

Without a systematic evaluation based on objective information, it is difficult for professionals to achieve social accountability. However, the Japanese healthcare system has been established through profit-sharing among specific groups, including the revision of the fee-for-service system, without fulfilling its social responsibility to weigh social advantage and costs objectively [7]. This system was formed on the basis of rapid economic growth after World War II and a pyramidal population structure.

With the slowdown in economic growth and the coming unprecedented aging society, it will not be possible to keep the current system anymore. Under these circumstances, reconfiguring the system only for a cost reduction will end up affecting its fair accessibility and the quality of the health care. First, whether the values of systematic evaluations based on verified data in the NCD will be suitable for the new society will be validated, and second, resource allocation and the development of a system structure to fulfill the values will be considered. The NCD was built as a platform not only for medical providers, but also for stakeholders, such as administrators, legislators and insurers, to allow them to provide better healthcare and to seek roles in collaboration. Using the nationwide platform, the collaboration among the stakeholders in Japan will also allow them to give useful suggestions to other countries that will face aging societies in the near future. We herein evaluate the significance and issues related to database initiatives that impact various aspects of society.

Social significance and issues related to the database initiatives

We herein evaluate the social impact of the clinical database initiatives from the perspectives of utility, feasibility and propriety standards [8]. The utility standard involves understanding the values of those involved in the initiatives, as well as those affected by it, determining their needs and evaluating whether services are offered that address these needs. The utility standard is assessed from the perspectives of (a) clarification of the central issue, (b) comprehension of the values of those involved, (c) comprehension of the process and outcomes and (d) consideration of the impact that the initiatives have. The feasibility standard relates to verifying whether the initiatives are realistic and economically reasonable. This standard is discussed herein from the perspectives of (a) political validity, (b) realistic progression, (c) project management and (d) resource use. The propriety standard relates to whether the initiatives are carried out lawfully and ethically and whether they pay due consideration to those affected by the results, as well as those involved in the initiatives. The propriety standard is assessed from the perspectives of (a) respect for basic human rights, (b) transparency and information disclosure and (c) maintaining balance.

The utility standard

The central issue

Just as the United States (US) Institute of Medicine identified the concept of "healthcare for the patient" as the chief provision of the twenty-first century medical revolution [9], patient-centric considerations are also an important aspect of future healthcare. Reducing medical costs is often a central policy issue in healthcare. However, the primary aim of healthcare should be to provide the best service to patients, rather than to curb medical costs [10]. High-quality healthcare services must be provided to patients, and considering how to design and coordinate practical approaches and the healthcare provision system, such as that for remuneration, is important to achieve this goal.

A key consideration when discussing the topic of improvements in healthcare quality is to define, understand and evaluate the quality that brings to fruition the values of the patients. The existence of "specialists" in various fields implies that a different result is expected when such specialists are involved in healthcare, compared with when non-specialists are involved. Thus, to fully grasp the quality of healthcare, the different effects that result from specialist involvement must be explained from the patient's perspective. Also important is the understanding of how each specialty is defined and the extent of their involvement. This can be achieved through continuous measurements and evaluations of the structure (e.g., human and material resources, organizational structure and operational management policy), the healthcare process (e.g., diagnosis/examinations, judging treatment indications, patient transport and admission and surgery/treatments) and healthcare outcomes (e.g., short-term mortality, complications, mid- and long-term prognoses and patient quality of life) for each specialty. In this context, the central goal of the NCD is to serve as the foundation for the development of a system that provides long-term, high-quality

healthcare by interfacing with the clinical setting in terms of systematic data collection and practical analyses.

The value of the NCD to stakeholders

Patients and the general public

The benefits of the NCD for patients and the general public include their ability to receive high-quality healthcare through the improvement of the healthcare service throughout Japan. This is achieved through directives by the NCD for improvement, with the clinical setting at the forefront. By reviewing the NCD data, patients can choose facilities that suit their preferences, whether it be the presence of board certified physicians of a relevant field, or the certification of a particular facility.

Health care providers

By unifying the standards of data management, health care providers in clinical settings can compare their approaches with peers throughout Japan and gain an understanding of where they stand. A risk-adjusted analysis based on nationwide data allows for one to determine and provide feedback on the information of the risks patients have beforehand. On the basis of these objective data, health care providers can then determine treatment indicators and obtain informed consent. Standardized information can be reformulated as case reports and shared at conferences. Moreover, the use of the NCD at individual facilities can reduce the burden of paperwork, for example, by providing clinical organizations with access to data for applications of certification, such as those required for board-certified physicians [11, 12]. By adding additional items and using data from one's own facility, clinical research may progress more efficiently.

Participating institutions

Facility reports, in which the severity-adjusted clinical performance of a facility is contrasted with nationwide data, are periodically sent to the participating institutions. These reports can describe the characteristics of each institution and elucidate the issues that require solution. Moreover, knowing one's position among peers allows for strategic planning and proper staff management. The mere fact that a facility participates in a benchmarking project that uses NCD data is in itself a means to ensure stable quality as a facility [13, 14].

Clinical organizations

Maintaining a clinical database as per the unified standards and definitions allows clinical organizations to improve their understanding of the actual performance of various fields, particularly when unified standards and definitions exist. Not only do unified standards increase the reproducibility of the collected data, they also ensure scientific accuracy. The large sample size offered by the database further paves the way for various types of research designs. Moreover, accurate information, as well as insight into the implementation status of various treatments and their effects, allows clinical organizations to provide policies and recommendations on the evidence-based board certification of physicians, their effective placement, improvement of their work environments and setting remuneration schedules. By serving as the driving force for efforts to improve the quality of healthcare, clinical organizations, as groups of specialists, can broadly appeal to the utility of certified facilities and the significance of board certified physicians to society, and at the same time, achieve accountability to society.

International collaboration is important to evaluate the quality of healthcare and produce meaningful results. The aim of the collaboration is to compare the incidence rates of diseases, the treatment trends and the outcomes and to identify factors that explain the differences. The NCD was developed in collaboration with the leadership of the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), which adopted a similar goal of developing a standardized surgery database for quality improvement and investigation. The core members of the NCD joined the meetings and seminars of the ACS NSQIP to discuss various issues related to a large clinical database, including the data collection methods, data feedback and public relations. In addition, the NCD implemented the same variables as those of the ACS NSQIP to facilitate future international cooperative studies. This collaboration is expected to lead to potential global benchmarking and further collaborative efforts to evaluate and improve clinical practices.

Pharmaceutical/medical device companies

Research collaborations with clinical organizations will allow pharmaceutical and medical device companies to more rapidly carry out trials and post-marketing surveillance of pharmaceutical products and medical devices. Trials based on the NCD will decrease the costs associated with clinical trials and provide opportunities to obtain information on unregistered patients, thereby improving the scientific quality of the research. Moreover, when randomization is ethically difficult, data from the cases in the clinical database can be used to generate a control group, making it easier to determine the effects of interventions. For post-marketing surveillance, information on the effects and use of medical devices and drugs is valuable

for the development and promotion of more effective drugs and devices.

Government and insurance companies

A lack of understanding regarding healthcare quality indicators may result in the provision of low-quality care that increases the overall costs because it results in expensive postoperative adverse effects and higher rates of complications and mortality. Previous studies have reported that decreases in the mortality rates and incidence of adverse events through benchmarking activities can help cut down medical costs [15, 16]. Therefore, taken together, the coordinated efforts of the NCD, which carries out clinically led benchmarking activities, may benefit the government and insurers.

Processing and reporting results

Benchmarking reports

As discussed above, a report is periodically distributed to participating facilities and provides data on each facility's severity-adjusted clinical performance in comparison with the national data. The report is formatted in a way that makes the patient characteristics evident. In the cardiac surgery field, a web-based program already provides feedback on severity-adjusted clinical performance [17]. Real-time feedback through the web provides an opportunity to observe changes within facilities and shifts in clinical performance instantaneously.

NCD and the board certification system

Data registered with the NCD can be used to design evidence-based board certification systems. In addition to easy tracking of clinical performance, source data acquisition will also become easier, as the system streamlines the need to apply for source data and its usage. Through appropriate data registration, it will also be easier for facilities to become certified or considered an "associated facility" by achieving stable performance. With an effective certification system, the clinical performance data required for the certification process can be readily obtained, and performance comparison and on-site audits using source data can be conducted. For the most part, the current Japanese system focuses on the clinical experience of board-certified physicians. Coordinating with the NCD may enable these organizations to operate on the basis of the parameters that better reflect the clinical reality, including the severity-adjusted clinical performance and the rate of use of appropriate clinical treatments.

Communication within the clinical settings

From various perspectives, including reporting the results of the data analyses, status of database operations, policy measures through the NCD, improvements in entry items and interfaces and supporting each facility's efforts, the NCD and facilities of various fields will need to share information and communicate to operate at an advanced level. Periodic meetings, such as symposia and scientific conferences, in addition to the use of the web and e-mail, provide opportunities to share information and increase awareness. Furthermore, the formation of region- or topic-specific groups will promote NCD-related activities. These activities will enable organizations to introduce and share the best practice recommendations in the participating clinical departments.

Progress reports to patients and the government

Periodic reports for patients and government officials will ensure the impartiality of NCD-related activities. To this end, the NCD has established a group of outside experts (e.g., patients and specialists of law and information) to provide such reports. Moreover, when outside organizations provide funding, conflicts of interest must be considered. When institutional support is required to provide high-quality healthcare, policy recommendations must be coordinated among the members of the government, legislature and patients.

Considering various influences

In addition to prioritizing and appropriately designing NCD benchmarking efforts in various disciplines, an understanding of the overall clinical performance and the temporal transition of clinical processes is important. For instance, when a new treatment is widely used, the database must be kept current to understand and follow the impact of this treatment. For clinical performance evaluations, if inter-facility differences in perioperative mortality become small, the focus will need to be placed on a different complication with a larger disparity between facilities, and initiatives that consider this new area of investigation will be needed. Negative influences must be considered as well. In other countries, different benchmarking stances have had a major impact on patient selection, for example, the treatment of critically ill patients may be avoided, or patients may be discharged early or transferred to different departments [18, 19]. Continuous assessment of the impact of the NCD may help to prevent such occurrences in Japan. When clinical organizations offer recommendations to the government or other institutions, the consequences and effects of these recommendations must be monitored. This would allow for

before-and-after comparisons of certified facilities with regard to patient transfer and the impact of certification on the clinical performance [20, 21].

The feasibility standard

Political validity

The NCD was established in April 2010 as a general incorporated association in partnership with several clinical organizations (http://www.ncd.or.jp). By participating as members of various NCD divisions, leaders of various organizations and those in charge of the board certification system can continuously guarantee partnerships with the leadership of various disciplines and the board certification system. However, NCD operations are free from the influence of other stakeholders, such as the government and businesses. Although donations from businesses and government research grants can help fund NCD-related activities, these are used in a manner that secures the independence of NCD operations.

Realistic progression

In order for NCD operations to continue successfully, it may be beneficial for the various specialty divisions to divide roles among themselves and to collaborate in performing the day-to-day operations. Independent NCD divisions are already in place for continuous coordination with the board certification system in each field. The data management and analysis secures the scientific quality of the data and analysis, systems management ensures the continuity and security of information systems and investigation of the legality and ethicality of activities aids in securing resources and preparing budget plans.

Particularly important is the development of a system that allows for easy data entry and reduces the burden on those entering the data. To this end, case registration in the NCD is based on an easy-to-use web system. The results of a questionnaire survey of various clinical departments registered with the NCD indicated that 63 % of respondents entered information directly via the web while referring to medical records (i.e., source data: Table 1), and 52 % entered information in real-time or immediately upon finalization of the information without delay (Table 2). Moreover, the survey revealed that data entry was performed at common hospital computer terminals or on individuals' personal computers in most cases. In 3.1 % of clinical departments, data entry was performed at an operating room computer terminal (Table 3); however, entering data onto the web while referring to source data was difficult for some departments. Therefore, information was written on paper first and entered into the system later (Table 1). The Case Report Form developed by the NCD is useful in such situations.

Table 1 The input method (multiple answers allowed, $n = 2,123$)

	n	%
Direct data entry via the Web while referencing medical records	1,344	63.3
Data entry after first accumulating data in the department's database (e.g., FileMaker, Access)	458	21.6
Data are first written on case report forms (CRFs; data entry manuals) and then registered	438	20.6
Departmental information systems, such as electronic medical charts, are first revised to be compatible with the NCD before data entry	175	8.2
Others	37	1.7

Table 2 Timing of data entry ($n = 2,123$; as of January 13, 2012)

	n	%
Register case information in real-time to the extent possible	503	24
Register case information upon finalization of information	598	28
Case information is collected and entered periodically	1,022	48

Table 3 Location of data entry (multiple answers allowed, $n = 2,123$)

	n	%
Common terminal other than a hospital terminal	1,156	54.5
Personal computer	1,081	50.9
Hospital terminal outside the operating room	325	15.3
Operating room terminal	65	3.1
Others	50	2.4

In order to avoid the burden on physicians, the NCD allows data entry by various medical staff members in each department. NCD data entry privileges allow people other than physicians to enter the data. Table 4 lists the data entry workers utilizing the NCD as of January 13, 2012. Although the department chair entered information in 58 % of the departments, a medical information manager entered information in 10.2 % and a medical administrative assistant did so in 35.1 % of departments. Importantly, either the department chair or a physician designated by the department chair must approve each case for data entry when somebody other than a physician enters the data to secure the data accuracy. Before the initiation of the database, tests were conducted in various relevant areas to determine the user needs. As a result, an easy-to-use

Table 4 Data enterer (multiple answers allowed, $n = 2,123$)

	n	%
Department chair	1,125	53.0
Department-affiliated physician (other than department chair)	1,232	58.0
Department-affiliated resident	113	5.3
Physician affiliated with different department	7	0.3
Nurse	13	0.6
Medical information manager	216	10.2
Medical administrative assistant	745	35.1
Others	60	2.8

system with an error identification component was developed. Efforts to improve the system continue today in the form of a questionnaire on the web that solicits comments on how to improve the system.

Management plan

A database cannot operate on its own if no data are entered, regardless of whether the system is ready for operation. As its name suggests, a clinical database requires the entry of technical and clinical information, which can be time-consuming. Securing funds for labor costs associated with data entry for each department is no simple task in Japan. Therefore, consistent with this, data are often entered by the physicians themselves. In the NCD, data entry is performed by workers of various backgrounds (Table 4). Continuous sharing of high-quality data requires the securing of funding and personnel to enter the data. In addition, the data must be verified. To address this issue, NCD-registered hospitals throughout Japan have been requested to provide continuous support and understanding of the processes involved in maintaining such a huge database. For example, large hospitals may perform examinations that might not be carried out at small-scale facilities. Therefore, data from such examinations cannot be included as entry items in the database. Thus, an important consideration is the verification of whether entry items and the entry system are realistic for each participating institution. Moreover, because the clinical database documents medical treatments, database items and options inevitably change with advances in surgery and changes in treatment. Depending on when the entry items are revised, the entered data may no longer be used; therefore, frequent revisions without careful planning must be avoided. This underscores the importance of entry item management.

Resource use

By unifying the standards and digitizing the medical record systems in each participating facility, the costs related to data collection may be minimized. In addition, incorporating a program that extracts clinical information other than that requiring a physician's judgment into the database would decrease the burden associated with data entry. In this way, the clinical database may be most efficiently developed in conjunction with developments in medical record systems.

The propriety standard

Respecting basic human rights and consensus building

Ethical guidelines and study types

The NCD is grounded on the framework of observational studies. Therefore, no additional tests or surgery, or even a prolonged length of stay, are required for the institution to participate, and the registration of patient information does not influence the treatments. Projects that do not involve documenting actual events are bound by the Ethical Guidelines for Epidemiological Research developed by the Japanese Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labour and Welfare [22]. For interventional studies, such as randomized-controlled trials, comprehensive registration in the NCD may be desirable [23]. In such cases, a new review based on the Ethical Guidelines for Clinical Research must be conducted [24]. Even within the framework of observational studies, broadening registration details and targeting certain disorders can change the nature of the management and operation of clinical databases. Changes that are particularly pronounced may warrant further ethical review, and project implementation may be reconsidered in light of independent valuations.

Patient consent

The patient intentions must be respected when considering the pros and cons of data registration. This can involve obtaining explicit verbal or written consent from participants (opt-in) [23], or not obtaining consent, but accepting a patient's explicit refusal to participate (opt-out) [25]. Only when these conditions are satisfied can clinical databases adopt the opt-out system. A few points are worth noting in this regard. First, clinical databases operate for the purpose of medical and public health research [26]. Second, clinical databases operate under the principle that the risk to participating patients is minimal [27]. Finally, clinical databases must guarantee that patients are given the opportunity to learn about the purpose of registration and the type of information registered [28]. The NCD has adopted the opt-out system and broadly discloses the

purpose of registration and the type of registered information. Moreover, to support the efforts of various clinical departments, the NCD provides web-based templates and explanatory material. However, when interventional studies (e.g., clinical trials) are conducted using the NCD infrastructure, a sufficient explanation must be provided to patients, and their explicit consent must be obtained.

Information security

The NCD data entry system is managed and operated via the web. Occasionally, a tradeoff may exist between the benefits of using the web and the associated risks, such as information leakage. The NCD data entry system uses an ID and password system, and the department chair of every participating facility has the authority to issue IDs. Users are notified about the password management policy; however, given that desirable security standards change as technology advances, the possibility that the evaluation standards at one point may not necessarily be valid in the future must be considered. In such situations, clearly articulating new policies on information management and operations is important. By complying with the disclosed policies, and the contents and measures therein, when issues arise, information system managers and operators can achieve a certain degree of accountability.

Use of personal information

Clinical databases must adhere to laws related to the protection of personal information. Various types of personal information, including (1) identifiable non-anonymous data, (2) identifiable anonymous data and (3) non-identifiable anonymous data require different considerations. In addition to patient information, the NCD includes information on participating facilities, as well as the health care providers involved in the treatment. Thus, the data management system and data use must be carefully considered. The American Association of Thoracic Surgery accepts analysis plans from applicants, and rather than source data, it principally feeds back the results of the analyses [29]. The Japanese Association of Thoracic Surgery has adopted a similar policy.

In view of the sensitivity of such information, the parent operating body of the NCD has established an ethics committee comprising outside experts. This committee includes members of the Japanese Surgical Society ethics board, lawyers, patient representatives and experts on information security. This ethics committee was requested to consider the ethical propriety of the entire initiative, and the progress of the review process was made public on the Japan Surgical Society website [30]. Thus, rather than merely undergoing a review, the contents of the discussion were made public, clarifying for the public the measures taken to address ethical issues. In addition, the NCD requested that the participating facilities undergo a review of ethical propriety regarding case registration in the form of facility director approval or a review from the facility's ethics committee. Because some participating facilities may not have ethics committees, the NCD made it possible to submit to a review by the NCD ethics committee. Since the review of ethical propriety must occur without delay, an application template was designed for ethics committee review and is available on the NCD website. As of January 2012, most participating facilities had received approval from a facility director.

Transparency and disclosure

Data usage

It becomes necessary to accept/adopt a fair stance for data usage. For example, in particular, covering up information that would be disadvantageous for certain facilities or businesses, or disclosing only advantageous information, may lead to conflicts of interest. Transparency must be guaranteed. Therefore, disclosure of information regarding the standards for data usage and rule of publication are important.

Publicizing the results of the data analyses

Further, the standards for publicizing the results of the data analyses need to be established. When performing severity adjustments, as in the US, where additional remuneration is provided on the basis of a department's clinical performance, the details and how severity adjustment is carried out must be disclosed [31]. In some cases, applicants who wish to use data may retain the results as internal documents without publicizing them. It is difficult to determine whether such decisions are made because secrecy would be advantageous, or whether the results are simply not worthy of public disclosure. However, certain standards need to be in place from the perspective of fairness.

Maintaining balance

Unifying the standards for evaluating clinical performance

Standards must be applied for evaluating the clinical performance of departments whose data are registered with the NCD. For instance, when choosing "mortality rate" as a clinical performance indicator, one facility may narrowly define the mortality rate as intraoperative mortality, whereas others may broadly define it as the 30-day postoperative mortality. Some facilities may even exclude periods in which an abnormally high number of deaths

Table 5 Participating facilities/number of departments (as of April 5, 2012)

	Facilities	
	n	%
Hokkaido/Tohoku	437	13.0
Kanto	942	27.9
Chubu	495	14.7
Kinki	650	19.3
Chugoku	252	7.5
Shikoku	142	4.2
Kyushu/Okinawa	454	13.5
Total	3,372	

occur. Even with raw mortality rates, the meaning differs between facilities that treat severe illnesses and those that only treat mild ailments. Therefore, the clinical performance must be fairly evaluated to avoid distrust among the participating facilities. Balanced information sharing can achieve this goal.

Fairness of participation

The NCD intends to improve the quality of healthcare throughout Japan. Because data registration is a condition for obtaining board certification, securing fairness is particularly important. In the US, many businesses pay millions of dollars each year to participate in clinical databases. However, in payment-based systems, the fairness of participation cannot be guaranteed, and coordination with board certification systems is difficult as well. Given the large number of small facilities in Japan, purchasing software for each department within a participating facility is not economically feasible. The NCD data entry software program was developed for use by all facilities and is distributed for free. Therefore, since the beginning of registration on January 1, 2011, more than 3,300 participating facilities have registered with the NCD as of April 2012 (Table 5).According to an administrative cross-country study of medical facilities by the Ministry of Health, Labour and Welfare, surgery under general anesthesia was conducted in 4,519 facilities in Japan [32]. The number of registered facilities by the Japan Surgical Society was 2,143 as of March 2012. [33] Therefore, a large proportion of the Japanese facilities in which surgeries are conducted participate in the NCD.

Conclusions

The coordination of a nation-wide clinical registry, such as the NCD in Japan, with board certification systems in various medical disciplines will positively impact society through their activities. The social implications of the activities must be considered. By identifying and addressing issues that arise from analyzing data, the clinical setting will drive improvements in healthcare quality. The central theme of clinical database activities is the provision of high-quality healthcare to patients and the general public. Clinical research and evidence-based policy recommendations based on the data from this database may positively impact businesses, the government and insurers. Initiatives may be evaluated to assess whether they are realistic and reasonably economical in comparison with the previous initiatives, in order to guarantee that they are conducted lawfully and ethically and to ensure that they pay due consideration to all the stakeholders involved. To ensure this, the continuity and responsibility of activities require continuous evaluation.

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Conflict of interest None of the authors have any conflict of interest.

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ORIGINAL CONTRIBUTION

Mortality After Common Rectal Surgery in Japan: A Study on Low Anterior Resection From a Newly Established Nationwide Large-Scale Clinical Database

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BACKGROUND: The health-care system, homogenous ethnicity, and operative strategy for lower rectal cancer surgery in Japan are to some extent unique compared to those in Western countries. The National Clinical Database is a newly established nationwide, large-scale surgical database in Japan.

OBJECTIVE: To illuminate Japanese national standards of clinical care and provide a basis for efforts to optimize patient care, we used this database to construct a risk model for a common procedure in colorectal surgery—low anterior resection for lower rectal cancer.

DESIGN: Data from the National Clinical Database on patients who underwent low anterior resection during 2011 were analyzed. Multiple logistic regression analyses were performed to generate predictive models of 30-day mortality and operative mortality. Receiver-operator characteristic curves were generated, and the concordance index was used to assess the model's discriminatory ability.

RESULTS: During the study period, data from 16,695 patients who had undergone low anterior resection were collected. The mean age was 66.2 years and 64.5% were male; 1.1% required an emergency procedure. Raw 30-day mortality was 0.4% and operative mortality was 0.9%. The postoperative incidence of anastomotic leakage was 10.2%. The risk model showed the following variables to be independent risk factors for both 30-day and operative mortality: BMI greater than 30 kg/m^2, previous peripheral vascular disease, preoperative transfusions, and disseminated cancer. The concordance indices were 0.77 for operative mortality and 0.75 for 30-day mortality.

LIMITATIONS: The National Clinical Database is newly established and data entry depends on each hospital.

CONCLUSIONS: This is the first report of risk stratification on low anterior resection, as representative of rectal surgery, with the use of the large-scale national surgical database that we have recently established in Japan. The resulting risk models for 30-day and operative mortality from rectal surgery may provide important insights into the delivery of health care for patients undergoing GI surgery worldwide.

KEY WORDS: Colorectal surgery; Epidemiology; Low anterior resection; National database; Risk factor; Risk model.

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Large-scale national clinical databases can illuminate national standards of clinical care and provide the necessary data for analyzing problems and evaluating potential solutions, thus serving as a basis for efforts to optimize patient care. Examples in the United States include the Surveillance Epidemiology and End Result–Medicare database[1] and the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP).[2] In Japan, a registry for gastroenterological surgery was established as a division of the National Clinical Database (NCD) in 2011 in cooperation with the Japanese Society of Surgery, Japanese Society of Gastroenterological Surgery, Japanese Society of Hepato-Biliary-Pancreatic Surgery, Japan Esophageal Society, Japanese Gastric Cancer Association, Japanese Society for Cancer of the Colon and Rectum, Liver Cancer Society Group of Japan, Japan Pancreas Society, Japan Society for Endoscopic Surgery, and Japanese Society for Abdominal Emergency Medicine. The NCD is a large-scale nationwide database, with data collected through a Web-based data entry system from an ethnically homogeneous population.

We chose a common but rather advanced procedure in colorectal surgery—low anterior resection for lower rectal cancer—as a model for investigating the usefulness of the NCD in the evaluation of surgical care. Colorectal cancer is the third most common malignant disease worldwide.[3] In Japan, colorectal cancer is the second most commonly diagnosed cancer, the third leading cause of cancer death in men, and the first leading cause of cancer death in women.[4] Since the 1980s, both the colon and the rectum have accounted for increasing proportions of cancer incidence in Japan.[4] Surgical intervention remains the primary treatment strategy for rectal cancer, and low anterior resection with preservation of the anal sphincter is a standard surgical procedure worldwide.[5] Thus, this procedure seems to be an appropriate choice for evaluating the levels of surgical care internationally. Because low anterior resection has been associated with relatively high morbidity and mortality,[6] the analysis of risk factors associated with this technique may help to improve the quality of surgical care, particularly in comparisons among countries.[7] We therefore constructed a risk model for prediction of the outcome of low anterior resection based on data from the NCD.

MATERIALS AND METHODS

Data Source

Since the establishment of the NCD, all new applicants for licensure in the surgical specialties accredited by the societies sponsoring the NCD are required to use records from this database to document their surgical experience. Thus, most hospitals, whether large or small, now participate in the NCD. In 2011, 3372 of 4883 (69%) hospitals with surgical departments participated. Although the NCD is basically a self-entry system, close attention is paid to maintaining the high quality of the entry data. Hospitals are advised to designate a data entry person (data manager) who completes the documentation of all cases treated in a given year through the Web-based data management system. Data managers participate in regular training programs at progressive levels. Instructions with definitions of all variables and inclusion criteria for the NCD are available to participating institutions on the NCD Website (http://www.ncd.or.jp/), along with an E-learning system to ensure the consistency of data input. All inquiries regarding data entry (approximately 80,000 inquiries in 2011) are answered, and a list of frequently asked questions is given on the Website.

Current laws, ordinances, and guidelines regarding the confidentiality of data are observed. Names of patients are not included in the database, and patients agree for their data to be included in research projects by using presumed consent with opt-out through the Web page and/or a notice of each hospital, which was approved by individual internal review board of all participating hospitals. A system for ensuring traceability of the data is in place, and regular audits are performed by designated NCD personnel, who visit institutions on a random basis for inspections validation of the data.

All cases of gastroenterological surgery are registered in the database, and detailed information is recorded for representative procedures. The recorded variables are strictly defined and are almost identical to those used in the ACS-NSQIP. Care is taken to ensure 30-day follow-up for outcomes.

Patients

National Clinical Database records for patients who underwent low anterior resection from January 1, 2011, through December 31, 2011, were analyzed for this study. The term low anterior resection limits the procedure to its cut-end (anastomosis) of the large intestine, which is lower than peritoneal reflection, and thus, the level of anastomosis is less than 7cm from the anal verge. Low anterior resection includes ultra-low anterior resection and intersphincteric resection with handsewn coloanal anastomosis. Records from patients who refused use of their data were excluded from the analysis. Records with missing data for age, sex, or status at postoperative day 30 were also excluded.

Outcome Assessment

The primary outcome measures of this study were 30-day mortality and operative mortality. Thirty-day mortality was defined as death within 30 days after the operation date regardless of whether the patient had been discharged from the initial admission. Operative mortality included all deaths occurring during the index hospitalization,

regardless of the length of hospital stay (up to 90 days), in addition to deaths occurring after hospital discharge but within 30 days after the operation date.

Morbidity within 30 days after surgery was also analyzed, regardless of whether a patient had been discharged from the initial admission. Morbidity was rigorously defined and categorized as wound, respiratory, urinary tract, central nervous system, cardiac, or other morbidity.

Statistical Analysis

A risk model was developed with patient and perioperative characteristics recorded in the NCD as potential predictor variables. Data were randomly assigned to 2 subsets, which were split 80/20; 1 subset was used for model development, and the other was used for a validation test. Two sets of logistic models (30-day mortality and operative mortality) were constructed for the development data set by using stepwise selection of predictors, with the p value for inclusion set at less than 0.05. A goodness-of-fit test was performed to assess how well the model could discriminate survivors versus deceased patients. Model calibration (the degree to which observed outcomes were similar to the predicted outcomes from the model across patients) was examined by comparing the observed with the predicted average within each of 10 equal-sized subgroups arranged in increasing order of patient risk. Receiver-operator characteristic curves were generated, and the area under the curve was used to calculate a concordance index (C-index), with a C-index value of >0.7 implying good prediction ability.

RESULTS

Demographic and Clinical Characteristics

From January through December 2011, 1,200,000 surgical cases were collected in the NCD throughout Japan. A total of 16,695 patients who had undergone low anterior resection were included in this study. The development data set included 13,316 records, and the validation data set included 3379 records. The patients' demographic and clinical characteristics are shown in Table 1. The mean age of the study population was 66.2 years; 64.5% were male. For 96% of patients, the indication for surgery was colorectal cancer. Disseminated cancer was diagnosed in 4.4%. The ASA score was grade 3 in 7.2%, and 3.9% required at least some type of assistance in daily life. Other preoperative comorbidities included chronic obstructive pulmonary disease in 2.5%, previous peripheral vascular disease surgery in 0.3%, and cerebrovascular disease in 3.5%.

Perioperative Variables

Preoperative and operative characteristics are given in Table 2. The operation was performed on an emergency basis in 1.1%. Preoperative radiotherapy was performed in 1.5% of the patients, and chemotherapy was performed in 1.8% of the patients. Although most procedures were performed with double-stapled anastomosis, handsewn anastomosis was performed in 4.1%. The rate of laparoscopic surgery was 39.2%, and a stoma was required in 4.6%. The median operative time was 237 minutes (range, 16–1199), and median blood loss was 160 mL (range, 0–16,300 mL).

Outcome Rates

As shown in Table 3, the raw 30-day mortality rate among the 16,695 patients who underwent low anterior resection was 0.4%, and the operative mortality rate (which includes 30-day mortality) was 0.9%. Complications including all grades that occurred within 30 days postoperatively were observed in 26.3% of the patients. Among these complications, 8.90% were grade 3 or higher. The rate of readmission within 30 days was 2.1%. Reoperation was performed within 30 days in 7.2%. Surgical site infections included superficial incisional infection in 4.6%, deep incisional infection in 1.5%, and organ space infection in 7.7%. The postoperative incidence of anastomotic leakage based on purulent discharge from a drain and/or on radiological leakage was 10.2%, whereas the majority of the cases presumably being performed were total mesorectal excision (TME).

Risk Model Results and Performance

Two sets of logistic models (30-day mortality and operative mortality) were constructed for the development data set and model calibration was examined by using a validation data set. Final logistic risk models for 30-day and operative mortality are presented with ORs and 95% CIs in Tables 4 and 5. There were 10 independent variables in the 30-day mortality model and 18 in the operative mortality model. Of these, the following 7 variables overlapped between the 2 models: older age category, previous peripheral vascular disease surgery, disseminated cancer, preoperative transfusions, BMI greater than 30 kg/m^2, platelet number less than $12 \times 10^4/\mu L$, and Na under 138 mEq/mL.

As shown in Table 6, the C-index (a generalization of the area under the curve) was 0.75 for 30-day mortality and 0.77 for operative mortality. The surgical mortality probability model exhibited reasonable discrimination and excellent calibration ($p < 0.001$) in the validation data set.

DISCUSSION

To our knowledge, this is the first report of a probability model of surgical mortality for a common rectal surgical procedure (low anterior resection) from the NCD, with a data set consisting of 16,695 consecutive cases within 1 year. In 2011, NCD collected more than 1,200,000 surgical cases from over 3300 hospitals nationwide in Japan,

TABLE 1. Demographic and clinical characteristics of patients who underwent low anterior resection in Japan during 2011 and outcome

		Operative mortality (n = 144, 0.9%)	
Clinical characteristics		*Mortality*	*p*
Age, y, mean (SD, median)	66.2 (11.7, 67.0)	–	–
Sex			
Male	10,772 (64.5)	110	<0.003
Female	5923 (35.5)	44	
Indication for surgery			
Malignant tumor	16,440 (99.7)	–	–
Appendix cancer	8 (0.05)	0	1.000
Colorectal cancer	16,032 (96.0)	140	0.666
Anal canal cancer	149 (0.9)	1	1.000
Carcinoid	96 (0.6)	1	0.566
GIST	18 (0.1)	0	1.000
Cancer metastases or relapse[a]	583 (3.5)	8	0.168
Benign tumor	71 (0.4)	2	1.000
No tumor[b]	184 (1.1)	2	0.674
Disseminated cancer[c]	733 (4.4)	25	<0.001
ASA-PS grade			
5	6 (0)	–	–
4	22 (0.1)	2[d]	0.024
3	1201 (7.2)	–	–
ADL (preoperative)			
Totally dependent	97 (0.6)	7	<0.001
Partially dependent	652 (3.9)	35	<0.001
COPD	424 (2.5)	12	<0.001
Previous PVD surgery	56 (0.3)	4	0.001
Bleeding disorder without treatment	72 (0.4)	6	<0.001
Cerebrovascular disease	579 (3.5)	13	0.002
Preoperative transfusions	249 (1.5)	17	<0.001
Smoked within the past year	3440 (20.6)	26	0.531
Habitual alcohol consumption	3938 (23.6)	35	0.850
BMI, kg/m^2 (N = 16,564)			
Mean (SD)	23.5 (70.6)	–	–
Distribution			
<25	13,192 (79.6)	–	–
25–30	2988 (18.0)	–	–
30–35	325 (2.0)	–	–
>35	59 (0.4)	–	–

N = 16,695. Values are numbers of patients with percentage in parentheses, unless otherwise noted.
–, not applicable; ADL = activities of daily living; ASA-PS = American Society of Anesthesiologists Physical Status classification; COPD = chronic obstructive pulmonary disease; GIST = gastrointestinal stromal tumor; PVD = peripheral vascular disease.
[a]Cancer metastases or relapse may overlap the headings of malignant tumors.
[b]Lower anterior resection performed for reasons other than malignant or benign tumor.
[c]Surgery resulted in incomplete resection.
[d] ASA-PS grade 4 and 5.

which may be the largest clinical data collection to date for surgery within 1 year. Most of the patients (96%) underwent low anterior resection for colorectal cancer. The 30-day mortality after low anterior resection in this series was 0.4%, which was much lower than results reported in other countries, for example, in 20,150 colorectal surgeries on nonelderly patients (<70 years) in NSQIP (2005–2007), the mortality was 2.0%.[8] In other multicenter studies, 30-day mortality was 5.8% to 6.8% (colorectal surgery; England), 2.4% to 7.0% (anterior resection; Norway), 2.1% (anterior resection; Sweden), 2.3% (rectal surgery; Belgium), 3.1% (rectal surgery; Spain), and 5.5% (elective colorectal surgery; United Kingdom).[9–13] The surgical mortality probability model exhibited reasonable discrimination and excellent calibration in the validation data set.

Differences exist between Japan and Western countries in the surgical management and neoadjuvant treatment of rectal cancers, including differences in the use of lymph node dissection and preoperative chemoradiation.[14] Lateral lymph node dissection, in addition to TME, is the standard operative procedure for lower rectal cancer in Japan.[15] However, the precise number of cases with lateral lymph node dissection in the current NCD data set is not known. The principle of complete lymph node dissection in rectal cancer surgery in Japan is to make a high central ligation up to the root of the inferior mesenteric artery. In

TABLE 2. Preoperative and operative characteristics and outcome

Characteristic	n/N (%)[a]	Operative mortality (n/N = 144/16,695, 0.9%) Mortality	p
Emergency operation	178/16517 (1.1)	7	0.001
Preoperative treatment			
Radiotherapy	254/16,695 (1.5)	1	0.729
Chemotherapy	299/16,695 (1.8)	5	0.117
Bleeding, mL, median (range), N = 16,403	160.0 (0–16,300)	3[b]	0.494
Blood transfusion, mL, median (range), N = 16,568	2441 (0–40,000)	27[c]	<0.001
Operation time, min, median (range), N = 16,580	237 (16–1199)	22[d]	0.990
Surgical procedure			
Handsewn anastomosis	677/16,695 (4.1)	4	0.668
Laparoscopic surgery	6541/16,695 (39.2)	38	0.002
Stoma creation	771/16,695 (4.6)	7	0.841

[a]Unless otherwise noted.
[b]Bleeding over 2000 mL.
[c]Blood transfusion over 5 units.
[d]Operation time over 6 hours.

contrast, the standard operative strategy for rectal cancer in Western countries is TME without lateral lymph node dissection; instead, preoperative chemoradiation treatment is added.[16] Neoadjuvant radiation was performed in only 1.5% of our patients. A randomized controlled trial is being conducted to compare TME alone with TME plus lateral lymph node dissection in stage II or III lower rectal cancer,[15] and we need a few more years to answer the question of whether lateral lymph node dissection provides an oncological benefit to the patients with low rectal cancer. Nevertheless, both lateral lymph node dissection and preoperative chemoradiation treatment may increase operative morbidity and mortality.[15]

It is interesting that a BMI greater than 30 kg/m^2 had the highest odds ratio (7.1) for 30-day mortality in our risk models. The relatively low BMI in our series (mean, 23.5; SD, 70.6 kg/m^2) might explain our relatively low operative mortality. Only 2.3% of our patients had a BMI greater than 30 kg/m^2. Reports have suggested that obese patients undergoing colectomy have higher postoperative morbidity and mortality.[17,18] However, according to an ACS-NSQIP report, 30-day mortality did not differ significantly by BMI in colectomy for cancer.[19] Another study showed that lateral lymph node dissection increased morbidity,[15] and this procedure may also have affected the mortality of the patients with obesity.[20,21]

The quality of a database depends on the robustness of data collected.[14] It is interesting that significant differences in colorectal procedures were observed between the ACS-NSQIP and ACS case log systems in risk factor and outcome data.[14] Although the spectrum of procedures presented was remarkably similar between the 2 programs, the case log system enabled surgeons to self-report patient

TABLE 3. Outcome of low anterior resection and operative mortality.

Outcome	n (%)[a]	Operative mortality Mortality	p
Mortality			
30-day	75 (0.4)	75	<0.001
Operative	144 (0.9)		
Readmission within 30 days	353 (2.1)	4	0.551
Reoperation			
Within 30 days	1195 (7.2)	45	<0.001
Any	1348 (8.1)	54	<0.001
Complications include all grades	4393 (26.3)	114	<0.001
Complications of grade 3 or higher	1487 (8.90)	95	<0.001
Surgical complications			
Superficial incisional SSI	763 (4.6)	17	<0.001
Deep incisional SSI	254 (1.5)	15	<0.001
Organ space SSI	1285 (7.7)	33	<0.001
Anastomotic leak	1700 (10.2)	50	<0.001
Pulmonary embolism	14 (0.1)	2	0.006
Urinary tract infection	229 (1.4)	13	<0.001
SIRS	194 (1.2)	8	<0.001

[a]N = 16,695.
SIRS = systemic inflammatory response syndrome; SSI = surgical site infection.

TABLE 4. Low anterior resection risk models: 30-day mortality

Characteristic	30-day mortality, OR (95% CI)
Older age category	1.34 (1.13–1.58)
Previous surgery for PVD	6.24 (1.39–28.00)
Disseminated cancer	4.89 (2.52–9.49)
Preoperative transfusions	5.36 (2.45–11.74)
BMI >30 kg/m^2	7.01 (2.79–17.62)
Platelet count <120 × 10^3/μL	5.02 (2.20–11.44)
Serum albumin <40 g/L	3.41 (1.75–6.63)
Na <138 mmol/L	3.58 (2.06–6.22)
Bleeding disorder without treatment	5.22 (1.54–17.68)
Serum urea nitrogen >25 mg/dL	3.58 (2.06–6.22)

PVD = peripheral vascular disease.

TABLE 5. Low anterior resection risk models: operative mortality

Characteristic	*Operative mortality, OR (95% CI)*
Older age category	1.41 (1.24–1.60)
Sex, male	1.92 (1.18–3.15)
Respiratory distress, any	2.91 (1.48–5.70)
ADL (preoperative), totally dependent	2.92 (1.22–7.01)
ADL (preoperative), partially dependent	2.5 (1.42–4.40)
Ascites, any	4.04 (1.82–9.00)
Previous surgery for PVD	5.79 (1.84–18.18)
Disseminated cancer	2.80 (1.55–5.07)
Preoperative transfusions	2.58 (1.26–5.29)
BMI > 30kg/m^2	1.522 (0.428–12.625)
Serum creatinine >265.2 μmol/L	4.00 (1.59–10.05)
Low hemoglobin (men <135 g/L, women <125 g/L)	2.60 (1.51–4.47)
High hematocrit (men >0.48, women >0.42)	3.56 (1.39–9.10)
Platelet count <120 × 10^3/μL	3.44 (1.67–7.06)
Serum albumin <25 g/L	2.71 (1.26–5.82)
AST >0.67 μkat/L	1.89 (1.07–3.32)
Na <138 mmol/L	2.54 (1.65–3.90)

ADL = activities of daily living; AST = aspartate aminotransferase; Na = sodium; PVD = peripheral vascular disease.

risk factors and the NSQIP used trained data abstractors for recording, with strict data collection methods. In this regard, the NCD pays much attention to keeping the quality of the data high. Although it is a surgeon's self-reported data, participating hospitals are obligated to designate data managers for data entry. The NCD regularly holds training sessions for data managers and ensures traceability of the data, strict definitions of variables, 30-day follow-up of outcomes, and regular audits for data validation.

A unique feature of the NCD database is that patients are registered from all types of hospitals throughout the country. Under the national health care system, most patients do not have to travel to the large hospitals in metropolitan areas, but go to the hospitals nearby. Thus, the patient population of NCD was not limited to the large, high-volume hospitals or academic centers but includes many small hospitals. Also the patient population consists of almost a single ethnicity. In addition, the environment of the health care system may influence the outcome of surgical care. In Japan, patients can stay in hospital relatively longer than in Western countries. Actually, the length of hospital stay of the patients (n = 16,282, missing value was 413) undergoing low anterior resection during the year of 2011 was 21 days (median), and the length of postoperative stay was 16 days (median). Thus, patients can receive thorough postoperative care and treatment of comorbidities during the hospital stay. Accordingly, our rate of readmission within 30 days is 2.1%, whereas reoperation within 30 days is 7.2%.

TABLE 6. Risk model performance metrics for low anterior resection

Risk model	*p*	*C-index*	*95% CI*
30-day mortality	<0.001	0.75	0.64–0.86
Operative mortality	<0.0001	0.77	0.67–0.86

C-index = concordance index.

The 30-day mortality rate is the most common definition of postoperative mortality in the surgical literature, probably because it is easy to follow up patients for this short duration. However, 30-day mortality may underestimate the true risk for death after colorectal surgery.[14,22] In fact, in the literature, the 90-day mortality rate is recommended as a standard outcome measure after colorectal surgery. Therefore, we assessed all operative mortality (90-day mortality) in addition to 30-day mortality. Although operative mortality was more than double the 30-day mortality, it was still satisfactory.

This study had several limitations. First, the NCD is a newly established, self-selected set of programs, and data entry is dependent on each hospital. Although training programs for data managers have been set up, mistakes in data entry may be made due to inexperience. Second, we cannot separate out other trends or programs and influences (local or national) that affect the quality of surgical care.[23] Other factors not included in our variables (for example, the extent of the surgeon's specialization or case volume[24] or subjective bias in evaluation of the patient's condition)[25] may be better predictors of the outcome of the surgical care. Third, the frequency of laparoscopic surgery in low anterior resection (39.2% in this study) has recently been increasing. Low operative mortality was observed in laparoscopic techniques compared with open techniques; however, operative procedure (open or laparoscopic) itself was not the independent risk factor for mortality. Further precise analysis of laparoscopic techniques on morbidity and mortality will be needed. Fourth, low anterior resection consists of a mixture of low-risk and high-risk procedures. For example, the anastomosis level (distance from the anal verge) was not included in our database. Thus, rectosigmoid colon cancer and low rectal cancer may both be included in the analysis. Fifth, although most hospitals nationwide participate in the NCD program, this was not a population-based study.

Nonetheless, studies such as this provide information about risks and benefits that are particularly relevant in surgery, where patients must make decisions as to whether to proceed with an operation and where and from whom they will seek care. Our results facilitate comparisons among surgeons and institutions within Japan, as well as comparison with other countries, thus serving as a catalyst for quality improvement and as a basis for accurate counseling of patients regarding operative risk.

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ORIGINAL ARTICLE

Nomogram Prediction of Metachronous Colorectal Neoplasms in Patients With Colorectal Cancer

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Objective: To construct a predictive model of postoperative colorectal neoplasm development using a nomogram.

Background: Although patients with colorectal cancer (CRC) are known to be at high risk of developing metachronous adenoma or CRC, no statistical model for predicting the incidence of postoperative colorectal lesions has been reported.

Methods: A total of 309 CRC patients who underwent surgical resection received regular endoscopic follow-up to detect the development of metachronous adenoma or adenocarcinoma. The patients were divided into the derivation set (n = 209) and the validation set (n = 100). The nomogram to predict the 3- and 5-year adenoma-free survival rates was constructed using the derivation set, and a calibration plot and concordance index (c-index) were calculated. The predictive utility of the nomogram was validated in the validation set.

Results: Sex, age, and number of synchronous lesions at the time of surgery for primary CRC were adopted as variables for the nomogram. The nomogram showed moderate calibration, with a c-index of 0.709 in the derivation set and 0.712 in the validation set.

Conclusions: A nomogram based on sex, age, and number of synchronous lesions at the time of surgery has the ability to predict postoperative adenoma-free survival.

Keywords: colonoscopy, colorectal adenoma, colorectal cancer, nomogram, postoperative surveillance

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Colorectal cancer (CRC) is one of the most common malignancies in Japan and in Western countries.[1] Furthermore, those with a history of CRC are at a higher risk for developing second metachronous adenomas or CRC recurrence during the follow-up period.[2–5] Chen et al[6] reported that 0.7% of patients develop metachronous CRC during the 3 years after surgical resection for the initial CRC.

It is generally accepted that most CRCs develop through a continuous process, transforming from normal mucosa to adenoma to carcinoma,[7–9] a process known as the adenoma-carcinoma sequence. Therefore, the early detection and endoscopic resection of newly developed adenomas constitute an important preventive strategy, especially in patients who have undergone surgical resection for primary CRC. However, there are no definite guidelines for adenoma surveillance after the surgical resection of primary CRC. The 2006 guidelines issued by the American Cancer Society indicate that a postoperative colonoscopy should be performed 1, 4, and 9 years after the initial surgical procedure,[10] but these guidelines also state that the currently available evidence does not fully address any clinical, genetic, or biologic markers that may predict the development of metachronous CRC. Therefore, the development of a prediction model of metachronous colorectal lesions after resection of initial CRC is very important.

Several studies have previously attempted to identify risk factors for the development of metachronous adenomas after resection of initial CRC. The location of CRC in the proximal colon and previous or synchronous adenoma presence were reported to be risk factors for the early development of metachronous lesions.[5,11] However, there have been no previous studies investigating the time course of adenoma formation after surgery using the log-rank test or Cox proportional hazard model. Recently, we demonstrated that age, presence of a synchronous lesion, and diabetes mellitus were independent predictive variables affecting the development of postoperative colorectal neoplasms.[11] By extending the previously reported regression results, we have designed the present study to construct a predictive model of postoperative colorectal neoplasm development using a nomogram, a tool widely used among clinicians because of its utility as a prediction model and its user-friendly interface.[12,13]

MATERIALS AND METHODS

Patient Selection

We retrospectively evaluated the medical records of 552 consecutive patients with colorectal adenocarcinoma, diagnosed between January 2004 and December 2007, who underwent surgical resection at the Department of Surgical Oncology, the University of Tokyo Hospital. Patients with adenomatous polyposis (>30 lesions at the time of surgery or familial adenomatous polyposis), those with hereditary non-polyposis colon cancer, and those with inflammatory bowel disease were excluded from the study. After surgical resection, all specimens were histopathologically reviewed, and the pathological TNM class and stage were determined according to the classification established by the American Joint Committee on Cancer.[14] In cases of multifocal disease, the histopathological variables were determined by assessing the dominant lesion (the most extensive lesion based on tumor invasion or size). Primary colon cancer located proximal to the splenic flexure was defined as right-sided, and the distally located one was defined as left-sided; all variables were assessed at the time of surgery. This study was approved by the institutional review board, and all patients gave written informed consent.

The first colonoscopy was scheduled at 1 year after surgery, and adenomas detected during the first colonoscopy were treated as synchronous lesions. Polyps larger than 5 mm were removed by endoscopic mucosal resection and were histopathologically analyzed. Hyperplastic polyps and other nonneoplastic colorectal lesions were recorded but not included in the analysis. After confirming the absence of colonic lesions (clean colon) by perioperative colonoscopy, endoscopic surveillance was conducted every 1 to 2 years. Patients who failed to undergo the second colonoscopy, which was usually scheduled 2 years after surgery, were excluded from the study; the final number of patients enrolled in this surveillance program was

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309. The patients were divided into 2 groups: the derivation and validation groups. The derivation group consisted of 209 patients who underwent surgery from January 2004 to June 2006, and the validation group consisted of 100 patients who underwent surgery from July 2006 to December 2007. The nomogram was constructed on the basis of derivation group data, and its predictive utility was validated in the validation group.

Statistical Analysis

The Kaplan-Meier method was used to estimate overall survival and recurrence-free survival, and the log-rank test was used to analyze differences in survival between groups. For the derivation group, the following potential prognostic variables were assessed: sex, age, and sex (general characteristics); tumor location, depth of invasion, regional lymph node metastasis, distant metastasis, lymphatic invasion, venous invasion, histologic differentiation, and the presence of concomitant CRCs and/or adenomas at the time of surgery (cancer-related variables); and smoking, body mass index greater than 25 kg/m^2, history of previous malignancies (CRC or extracolic malignancy), first-degree family history of CRC, hypertension, hyperlipidemia, and diabetes mellitus (patient background variables). A multivariate Cox proportional hazards analysis was performed using variables whose P value was less than 0.2 in univariate analysis. By following the method of Wang et al,[15] we built nomograms for predicting the probability of 3- and 5-year adenoma-free survival rates after surgery. The nomogram was subjected to 100 bootstrap resamples for calculating the estimated Harrell concordance index (c-index) as an index of model performance.[16] The c-index estimates the probability of concordance between predicted and observed outcomes in rank order and is equivalent to the area under the receiver operating characteristic curve, if there are no censored cases.[16] It represents the ability of the model to discriminate between patients who survived without adenoma development and those who did not. Higher values indicate better discrimination: a value of 0.5 indicates no predictive discrimination, whereas a value of 1.0 indicates perfect separation of patients with different outcomes.

We also performed calibration using a calibration curve, a graphic representation of the relationship between the observed outcome frequencies and the predicted probabilities, with both the derivation and validation groups. Using the constructed nomogram, the score of predicting the 5-year adenoma-free survival rate was calculated for both groups. All statistical analyses were performed using the statistical software program R 3.0.1 with rms and Hmisc packages (http://www.r-project.org/).

RESULTS

Of the 552 patients enrolled in the study, 243 were excluded for the following reasons: 227 patients did not undergo colonoscopic surveillance (CRC progression in 108 patients, other disease progression in 64 patients, and a move or change of hospital in 55 patients), 4 patients had colitic cancers, 3 patients had polyposis, and 3 patients died during the perioperative period. The differences between the included and excluded patients are presented in Table 1. Because a large proportion of the patients excluded from the analysis had residual cancer or recurrence, and most of the remaining excluded patients failed to receive surveillance because of the development of diseases other than CRC, the age and stage of initial CRC were higher in the excluded group than in the included group. General characteristics related to adenoma formation are also presented in Table 2. The characteristics of patients in the derivation and validation groups were comparable. The incidence of CRC formation per year was 0.0064 in both groups, and that of adenoma formation was approximately 0.084 in both groups. Although the 5-year adenoma-free rate was a little lower in the validation group, this difference was not statistically significant ($P = 0.077$).

TABLE 1. Differences Between Included and Excluded Patients

	Included	Excluded	P
Total, n	309	243	
Sex, n			
Male	199	149	
Female	110	94	0.4564
Age, mean ± SD, yr	63.2 ± 10.3	68.0 ± 11.7	<0.001
Location, n (%)			
Right hemicolon	68 (22.0)	78 (32.1)	
Left hemicolon	112 (36.2)	76 (31.3)	
Rectum	129 (41.7)	89 (36.6)	0.0288
Stage, n (%)			
0/I	99 (32.0)	45 (18.5)	
II	105 (34.0)	69 (28.4)	
III	84 (27.2)	70 (28.8)	
IV	21 (6.8)	59 (24.3)	<0.001

TABLE 2. Patient Characteristics

	Derivation Data Set	Validation Data Set
No. patients	209	100
Sex, n (%)		
Male	134 (64.1)	64 (64)
Female	75 (35.9)	36 (36)
Median follow-up time, yr	5.57	5.04
Total follow-up time, yr	1097.0	466.5
Total colorectal cancer cases developed during follow-up time, n	7	3
Incidence per year	0.00638	0.00643
Total colorectal adenoma cases developed during follow-up time, n	93	39
Incidence per year	0.08470	0.08359
Cumulative 5-yr adenoma-free rate	75.35%	71.71%
95% CI	68.31–81.25	61.30–80.22

CI indicates confidence interval.

Development of the Nomogram

The results of the univariate and multivariate analyses of the association between variables and the 5-year adenoma-free survival rate are shown in Table 3. In the univariate analysis, male patients and older patients had a significantly shorter adenoma-free survival time. The variables associated with progression of the primary cancer, such as T stage and presence of lymph node or distant metastasis, showed no correlation with postoperative adenoma development, consistent with our previous report. Although the presence of second or additional primary CRC showed no correlation, if both synchronous CRC and adenomas were included in the category sublesions, the presence of sublesions was strongly associated with postoperative adenoma development. We previously reported that the presence of diabetes mellitus correlated with postoperative development[11]; however, in this study, no variables concerning patient background, including diabetes mellitus, correlated with adenoma development.

Therefore, we performed multivariate analysis using the variables of sex, age, and the presence of concomitant colorectal

TABLE 3. Univariate and Multivariate Analyses of the Association Between Clinicopathological Factors and Postoperative Adenoma-Free Intervals

	Univariate Analysis		Multivariate Analysis		
	5-yr Adenoma-Free Survival	*P*	Hazard Ratio	95% CI	*P*
Sex					
Female	84.5%				
Male	68.2%	0.0404	1.75	0.89–3.71	0.1102
Age					
<70 yr	76.6%				
≥70 yr	62.4%	0.0188	1.95	1.04–3.54	0.0387
Cancer-related variables					
Tumor location					
Right-sided colon	74.9%				
Left-sided colon	74.6%				
Rectum	73.1%	0.7888			
Depth of invasion					
T1/2	72.7%				
T3/4	74.1%	0.9003			
Regional lymph node metastasis					
N0	72.2%				
≥N1	76.9%	0.3909			
Distant metastasis					
M0	73.3%				
M1	80.9%	0.503			
Lymphatic invasion					
Absent	74.5%				
Present	71.4%	0.8254			
Venous invasion					
Absent	73.9%				
Present	74.3%	0.957			
Histopathology					
Well or moderate	73.0%				
Other	90.9%	0.106	2.54	0.54–45.43	0.2874
Concomitant colorectal cancers at the time of surgery					
Absent	75.0%				
Present	64.0%	0.1367	1.45	0.66–2.93	0.3394
Concomitant colorectal cancers and adenomas at the time of surgery					
Absent	84.2%				
Present	61.0%	<0.0001	1.95	1.04–3.54	0.0387
Patient background variables					
Smoking					
Absent	77.6%				
Present	69.2%	0.1768	1.23	0.69–2.23	0.4825
Body mass index ≥25 kg/m^2					
Absent	72.2%				
Present	77.2%	0.5937			
History of malignancies					
Absent	74.8%				
Present	64.6%	0.1307	1.39	0.60–2.81	0.4158
Family history of colorectal cancer					
Absent	72.6%				
Present	83.8%	0.2803			
Hypertension					
Absent	77.2%				
Present	66.8%	0.0994	1.03	0.57–1.91	0.9314
Hyperlipidemia					
Absent	74.3%				
Present	69.6%	0.6153			
Diabetes mellitus					
Absent	75.4%				
Present	66.9%	0.399			

CI indicates confidence interval.

sublesions. Because the latter 2 variables were independent predictive factors in the prediction of adenoma development and sex also showed a trend toward correlation, we constructed the nomogram with point scales of these 3 variables (Fig. 1). The sum of the each variable point was plotted on the total point axis, and the estimated median 3- and 5-year adenoma-free survival rates were obtained by drawing a vertical line from the plotted total point axis straight down to the outcome axis. The c-index of this model was 0.709, indicating good discrimination. Figure 2A shows the calibration graph for the nomogram, in which the probability of 5-year adenoma-free survival as predicted by the nomogram is plotted against the corresponding observed survival rates obtained by the Kaplan-Meier method. This illustration demonstrates good calibration of the nomogram. Furthermore, the derivation group was further stratified into 3 groups according to the score calculated using the nomogram: the high-risk (>75th percentile of the group), low-risk (<25th percentile), and intermediate-risk (25th–75th percentile) groups. Figure 3A demonstrates that scoring with the nomogram effectively discriminated the risk of postoperative adenoma development.

Validation

To validate whether the nomogram would be applicable to other data sets, we conducted a validation study using data from the 100 CRC patients in the validation group. The c-index of the validation group was 0.712, demonstrating that the nomogram also showed good prediction in the validation patient group. Moreover, the calibration plot of the validation group demonstrated good calibration (Fig. 2B). Patients in the validation group were also stratified by percentile into

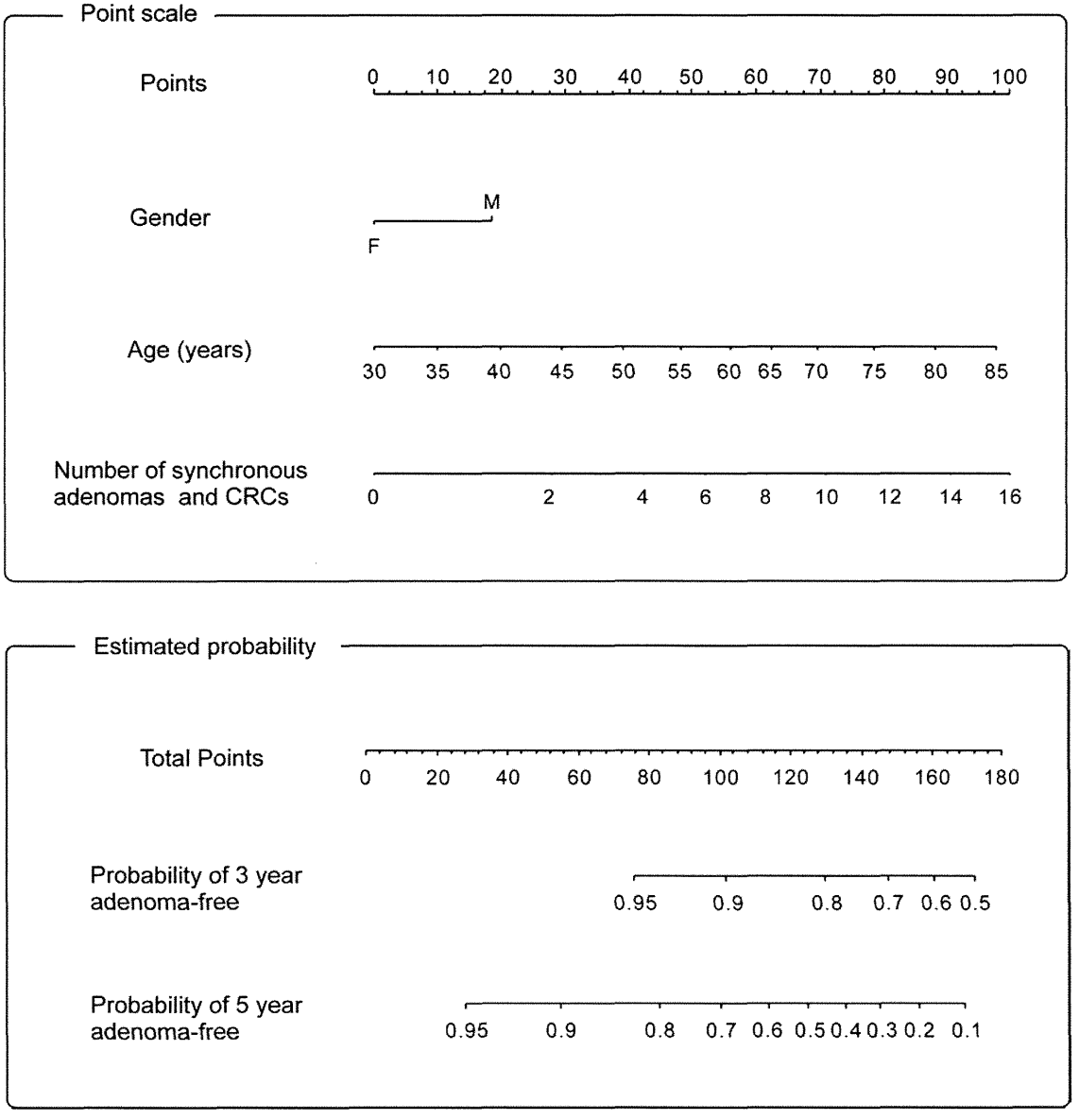

FIGURE 1. Nomogram for predicting postoperative adenoma-free survival after surgery for colorectal cancer. The 3- and 5-year probabilities of survival without adenoma or CRC development is estimated by summing the score of the 3 variables, that is, sex, age, and the number of synchronous adenomas and CRCs at the time of surgery.