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EBM-Based Clinical Practice Guidelines

Hideya SAKURAI

Executive Member, Board of Trustees, Japan Medical Association

Key words: Evidence-Based medicine; EBM; Medical technology; Clinical practice guidelines; Professional freedom

Introduction

The need for clinical practice guidelines that are grounded in evidence-based medicine (EBM) is a subject that has recently come under debate in various quarters. It goes without saying that this does not mean that the physicians of this country have been diagnosing and treating patients without evidence to date. Every medical institution and every physician collects and accumulates a variety of evidence, which they then evaluate before feeding it back into characteristic settings. Decisions on the policies (guidelines) of an individual institution or physician are made as the need arises and are then used as the basis for diagnosing and treating patients. There is no need for this process to be altered in the future.

Healthcare is first and foremost a highly individualized practice and the individual predicaments and value decisions of patients cannot be eliminated no matter what form guidelines may take. Nonetheless, the necessity of creating clinical practice guidelines that are founded in EBM as a way of maintaining and improving the quality of healthcare is widely recognized.

This article examines and elucidates a number of issues relating to the work that is being done by the nation and by the Ministry of Health, Labor and Welfare in connection with EBM-based clinical practice guidelines and the measures being taken by the Japan Medical Association (JMA), and simultaneously puts forward the opinions of the latter Association.

Study Group on the Positioning of Medical Technology Assessment (former Ministry of Health and Welfare)

Medical technology assessment as a technique for improving the quality of medical practice and patient services has been attracting attention in a number of countries, and it became clear that Japan would also need to investigate the introduction of this type of assessment. Bearing this situation in mind, in December 1996, the then Ministry of Health and Welfare (currently the Ministry of Health, Labor and Welfare) established the “Study Group on the Positioning of Medical Technology Assessment”. Akihiko Koike, then executive member of the Japan Medical Association, participated in the investigations of the study.
In June 1997, the study group finalized a report, which can be summarized as follows:
1. A definition of medical technology assessment
2. The position of medical technology assessment and related areas
3. The current status of medical technology assessment
4. The utilization of medical technology assessment in Japan
5. The need to tackle the promotion of medical technology assessment

Having received this report, the then Ministry of Health and Welfare established the “Study Group on the Promotion of Medical Technology Assessment” in June 1998 with the aim of investigating specific promotion measures for medical technology assessment.

**Study Group on the Promotion of Medical Technology Assessment (former Ministry of Health and Welfare)**

Takashi Aoyagi, an executive board member of the Japan Medical Association, participated in the investigations of this study group on behalf of the Association.

It is significant that one of the stated objectives of establishing this study group was that “Realizing evidence-based medicine (EBM) is crucial to the effective utilization of limited medical resources and to improving the quality of medical practice and patient services . . . ”. In fact, the discussions that were conducted by this study group converged on matters relating to EBM.

Generally speaking, the practice of EBM is conducted in four stages. The sequence is as listed below.
1. Clinical questions concerning a particular patient are elicited.
2. A search for literature that deals with these questions is undertaken.
3. The reliability of the literature obtained is appraised.
4. The appropriateness of applying the results from the literature to the patient is evaluated.

Clinical practice guidelines grounded in EBM are designed to enhance the efficiency of this process and to support physicians in diagnosing and treating patients. Based on these perspectives, the study group issued a report in March 1999, which is summarized as follows.
1. Promote EBM
2. Create medical (clinical practice) guidelines
3. Systemize activities towards comprehensive promotion
4. Promote clinical research and obtain the understanding and cooperation of the general public
5. Ascertain the necessity for an information network

**Bureaucratic Initiative in the Creation of Clinical Practice Guidelines**

Having received the suggestions of the “Study Group on the Promotion of Medical Technology Assessment”, plans were laid for the compilation of clinical practice guidelines to be undertaken as a bureaucratic initiative led by the then Ministry of Health and Welfare. The Ministry’s scientific research funds were to be utilized to support the creation of “Clinical Practice Guidelines” for individual diseases by various medical societies. In fiscal 1999, guidelines were compiled for among others, hypertension, bronchial asthma, myocardial infarction, and prostatic hyperplasia. This was followed, in fiscal 2000, by the provision of national support in the formation of guidelines for gastric ulcer, cerebral infarction, cataracts, low back pain, chronic rheumatoid arthritis, subarachnoid hemorrhage, and allergic rhinitis (hay fever).

Although the work of formulating the guidelines was being conducted by medical societies, the fact that the source of the funding (costs) was the country (government) created a number of problems. The societies were saying that the guidelines had been created by them, whilst at the national level, the government was saying...
that the guidelines had been created by it. This made it difficult to aver that regional healthcare settings and the circumstances of patients were being considered, meaning that the guidelines took on a “top-down” approach, and there was even a risk that they would be detrimental to the content of regional healthcare.

In addition, the Ministry of Health and Welfare’s budget allocation for fiscal 2000 included plans to establish databases for the literature relating to EBM and clinical practice guidelines within government facilities, and the management of EBM to be undertaken by the government. As might be expected, such unequivocal plans were indicated to be problematic even within the parliament, and the plans were withdrawn.

Clinical Practice Guidelines Information Center Project Committee (The Japan Medical Association)

In response to these movements, the Japan Medical Association exerted its influence over the Japanese Association of Medical Sciences (JAMS) and various hospital associations, overseeing the inauguration of a project committee targeting the establishment of a private-sector based “Clinical Practice Guidelines Information Center (tentative name)” that would be led by the Japan Medical Association. The deliberations of this committee yielded a number of conclusions.

1) The biggest problem is sifting through vast amounts of data for useful information that is in line with EBM and this is what underpins the formulation of appropriate clinical practice guidelines.

2) The clinical guidelines created by individual medical societies and others, on the basis of selected data or data obtained from original research, need to undergo a second evaluation. Appraising and judging whether or not the guidelines are objective and measure up to clinical results and achievements in this country is a major responsibility. It is a task that will require the recruitment of suitable human resources, including clinical physicians, clinical epidemiologists, and statisticians, and in which the Japan Medical Association must take a primary role.

3) Even after such assessments have been completed, the objective of clinical practice guidelines, even published guidelines, is ultimately to provide a source of reference. The guidelines should not impose any restrictions on the practice of physicians.

4) Clinical practice guidelines are not designed to be used by physicians only; their contents should also be shared with the patients who are on the receiving end of medical treatment.

5) Once a set of clinical practice guidelines has been created, continuous review that incorporates the feedback of opinions from practicing physicians and patients will be essential. As a starter, the project committee is currently engaged in formulating standards for the creation of clinical practice guidelines (i.e. guidelines for guidelines).

Study Group on the Healthcare Information (Ministry of Health, Labor and Welfare)

The Ministry of Health, Labor and Welfare, having jettisoned plans to establish EBM databases within national facilities, inaugurated the “Study Group on the Healthcare Information” in April 2001, with the aim of seeking a new direction for EBM. I participated in this study group on behalf of the Japan Medical Association. The study group has put forward the following items as matters for investigation.

1. On the information services required in healthcare settings in order to provide diagnosis and treatment

(1) What type of systems do specialist physicians require?
(2) What type of systems do general clinicians require?
(3) What types of systems do trainee doctors require?
and medical students require?

2. On specific measures for the required information services
   (1) How should the accumulation and processing of medical literature and guidelines be undertaken?
   (2) How should statistical evaluations relating to individual topics be undertaken?
   (3) On the operation of information services
       (a) What should be done regarding the contents of systems that should be disclosed?
       (b) How should the accumulation of useful data be undertaken?
       (c) How should the systemization of accumulated data be undertaken?
       (d) How should systemized data be presented?

3. On the division of roles between the private and public sector in relation to information services
   (1) What type of system should be put in place to move forward with the information services?
   (2) What role should the government take?
   (3) What role should the private sector take?
   (4) What support should the government extend to the private sector in its role?

Clinical Practice Guidelines Information Centers in Various Countries

An examination of one of the materials produced by this study group, which deals with organizations that are similar to clinical practice guidelines information centers in five countries, their establishing bodies, the types of databases available, and the bodies responsible for their administration, yielded the information shown in Table 1.

The following three points were confirmed as being basic concepts for the development of EBM databases in this country. (1) The need to ensure comprehensiveness, currency, objectivity, impartiality, and transparency. (2) The need to ensure free-access, including that by patients. (3) The need to ensure a secure financial base. It was also established that a number of additional points need to be considered, namely, (1) the necessity of promptly
developing the necessary systems for EBM, starting with databases, (2) the necessity of gaining respect for guaranteed academic impartiality, and to eliminate any unnecessary intervention by the administration, etc.

These considerations gave rise to three plans pertaining to the form that the body responsible for administering EBM databases in Japan should take, which were submitted by the study committee (Table 2).

**The Japan Council for Quality Health Care**

The result of the investigations outlined above was the decision to commission the “Japan Council for Quality Health Care”, currently a public-service corporation, to organize the EBM databases in this country.

The main reason for entrusting this task to the Japan Council for Quality Health Care was that the council is a neutral public-service corporation. However, at the same time, a number of other reasons were advanced including the fact that the “Assessments of the Quality of Health Care in Hospitals” that are currently being undertaken by the council also represents one facet of the “Medical Technology Assessments” that instigated the current problem, and are, moreover, closely related to “EBM-based Clinical Practice Guidelines”. In addition, the collection of medical information for inclusion in EBM databases can also be utilized in future assessments of the quality of health care in hospitals, and conversely, the medical information obtained from the hospitals that are subject to functional appraisal will be useful as evidence from clinical settings, in reviewing the EBM-based clinical practice guidelines.

In response to the proposed commission, the Japan Council for Quality Health Care held a hearing in December 2001, which resulted in their decision to accept the commission. Accordingly, as one of its projects, the council was requested to begin organizing EBM databases as of April 2002.

This represents one direction, which has been hammered out after long years of deliberations, however, this important project has still only just begun and there is no doubt that numerous problems lie ahead. This is a matter of great consequence to the Japan Medical Association and we intend to keep close tabs on this important project to ensure that it develops along the right tracks.

### Table 2

<table>
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<tr>
<th>Administrative Body</th>
<th>Financing</th>
<th>Points for consideration</th>
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| **JMA’s Clinical Practice Guidelines Information Center Plan** | Japan Medical Association | Japan Medical Association | *Problem of ensuring the impartiality of the project*<br>*Problem of patient access*<br>*Will it be possible to shoulder the enormous operating costs involved?*
| **A neutral institution** | Case assuming an existing public-service corporation | Treasury subsidy + private sector expenditure | *Treasury subsidies to public-service corporations are likely to be shelved, thus there is a problem of securing operating costs*
| Case assuming the establishment of a new public-service corporation | Treasury subsidy + private sector expenditure | *As above*<br>*Establishing a new nonprofit corporation is highly problematic*
| **Publicly-funded, privately operated** | Established by the government, operated by the private sector | Private sector commission using public funds | *Will government involvement intensify to the point of excess?* |
I would now like to present two problems that I perceive in connection with the practice of EBM.

**EBM Evidence**

The concept of practicing medicine based on evidence is one that is not open to debate. The following are proposals that have been put forward for classifying the quality of that evidence.

Classifying the quality of evidence  
(United States Preventive Services Task Force)  
I: Randomized controlled trials  
II-1: Epidemiological (nonrandomized) controlled trials  
II-2: Cohort studies and case-controlled studies  
II-3: Longitudinal studies, non case-controlled studies  
III: Opinions of leading medical authorities, epidemiological statements

In other words, enormous emphasis is placed on evidence that is based on epidemiological processes. However, whilst acknowledging the significance of evidence, it is possible to conceive a number of slight problems with this approach.

One example can be found in the report mentioned earlier that was issued by the Study Group on the Promotion of Medical Technology Assessment. The report gave prominence to the necessity of promoting EBM and stated that “In order to generate a scientific basis [for EBM] it is necessary to convert current pathophysiologically-focused studies into research that resembles randomized controlled trials that target patients”. I believe that this statement is erroneous. “Converting” medical research that is “pathophysiologically-focused” into “research based on randomized controlled trials” is not plausible in the field of medicine. If by this they mean the introduction of “research based on randomized controlled trials” that are grounded on “pathophysiological research” then that is understandable, but I am utterly opposed to “converting” the latter into the former.

As another example, in 2001 “A” tablets were approved as an analgesic agent for migraines. The results of the clinical trial with this drug, which employed the double-blinding method, was a headache improvement rate of 48.6% for the placebo group ($n=70$) and 71.5% for the “A-treated” group ($n=70$), or a significant difference, which was used to demonstrate that the drug “is fast-acting and has superior efficacy in the relief of pain from migraine headaches”, and it was approved as a new agent. However, put simply, the results of the trial were equivalent to efficacy in 5 patients out of 10 in the placebo group and 7 out of 10 in the “A-treated” group. Undeniably, this evidence is from a high quality randomized controlled trial and the difference is statistically significant, nevertheless, there are elements that are unsatisfactory. Five of the 10 patients who took “A” tablets actually experienced headache relief as a result of the placebo effect, thus it is conceivable that the headache was alleviated by “A” tablets in only 2 patients.

Evidence, as it is understood within the framework of current medical knowledge, is not that infallible. The report by the Ministry of Health, Labor and Welfare starts by interpreting EBM as being “healthcare that is based on scientific grounds”; somewhere along the line, however, this becomes simply, “healthcare that is reliably based”. I would even go so far as to suggest that it might be more fittingly interpreted as “healthcare that is based on the highly unreliable grounds of the scope of current knowledge”.

**Conclusion—The Professional Freedom of Physicians—**

I believe the view that physicians implement self-serving treatment, that this is a professional freedom granted to doctors, and that physicians are free to use their discretion, is wrong.
Although at the same time, I am also against the opinion that physicians must follow guidelines to the letter when treating their patients. In the long run, the purpose of the guidelines is to furnish a source of reference. Individual medical institutions and physicians must determine the advisability of adopting the guidelines, and even assuming that there are some physicians who do not follow said guidelines, such physicians should not immediately be labeled as “wrong”. In particular, under no circumstances should the guidelines be used as screening criteria for the healthcare services provided under the health insurance system.

On the other hand, the professional freedom of physicians should be considered to be an obligation, not a right. Physicians have an obligation to conscientiously and judiciously provide their patients with the best available healthcare, which should be based on evidence they themselves have judged. This is the discretion that physicians exercise, or their professional freedom. It is imperative that physicians do not wave aside this obligation in the face of pressure from outside. It is the patients who have the right to be provided with the best available medical treatment based on professional freedom.
JGCA Gastric Cancer Treatment Guidelines—A new trend in cancer treatment—

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Abstract: “General Rules for Gastric Cancer Study,” published by the Japanese Gastric Cancer Association (JGCA), has contributed greatly to advances in both the diagnosis and treatment of gastric cancer in Japan. In March 2001, the Association published a new book, “Gastric Cancer Treatment Guidelines,” a set of guidelines prepared by a committee of the Association. This is the first time in Japan that guidelines have been published for the treatment of cancer. These guidelines are expected to promote evidence-based medicine in the field of gastric cancer. In addition, an explanation of the guidelines for the patients and their families was published last December. This book provides clear, easy-to-understand information for the general public and may point to a new trend in the practice of cancer treatment.

Key words: Gastric cancer; Guidelines; EBM; Standard therapy; Japanese Gastric Cancer Association

Introduction

Gastric cancer is the most frequent type of cancer in Japan, with about 100,000 new cases occurring each year. Because of improved diagnostic techniques and more widespread screening, early gastric cancer has begun to account for a larger proportion of all gastric cancer cases, resulting in improved overall therapeutic results.

Standard gastrectomy, which involves resection of most of the stomach and extensive dissection of lymph nodes, was formerly a common procedure in the treatment of gastric cancer. However, as early cancers have increased relative to more advanced cases of gastric cancer, this treatment has begun to be reconsidered. Specifically, modified surgery involving limited resection of the stomach, preservation of the vagal nerve to avoid decreased postoperative function, and reduced dissection of lymph nodes have been tried. In addition, treatment by endoscopic mucosal resection (EMR) has been aggressively carried out in
patients with gastric cancer unlikely to be associated with lymph node metastasis. Laparoscopic gastrectomy, rather than open abdominal surgery, has also been used. On the other hand, for advanced gastric cancer, more extensive lymph node dissection including the para-aortic lymph nodes has been attempted. In addition to these modifications, chemotherapy, which previously had no substantial effect, has gradually become more beneficial because of new developments in dosing methods and improved drugs. In summary, the treatment of gastric cancer has been transformed from a conventional, fixed pattern of extensive resection and wide-ranging dissection to include increased variety and complexity.

These changes have created confusion among both doctors and patients as to the policies of treatment for gastric cancer. To clarify this confusion, the results of previous and current treatments need to be evaluated, and attempts to establish standard treatments appear necessary at this juncture. This paper provides an outline of the “Gastric Cancer Treatment Guidelines” issued by the Japanese Gastric Cancer Association (JGCA) in March 2001, and describes their significance.

Background

Although it is well accepted both within Japan and abroad that the treatment of gastric cancer in Japan ranks among the best in the world, treatment policies vary greatly among institutions. It is surprising to consider that no established policy of treatment exists for a disease that affects 100,000 persons per year. At a luncheon seminar of the Japan Surgical Society held in 1998, the author had the opportunity to give a presentation entitled “A Call for the Standard Treatment of Gastric Cancer.” On that occasion, the author offered the following three suggestions: first, that the “General Rules for Gastric Cancer Study,” which stipulate the staging of gastric cancer, not be altered frequently; second, that a questionnaire survey be administered to understand the present status of gastric cancer treatment; third, based on the understanding gained from the survey, that a standard treatment for gastric cancer be formulated on the basis of a thorough review of existing scientific evidence.

In addition, Dr. Toshifusa Nakajima, vice-president of the Cancer Institute Hospital, had evidenced great interest in formulating a standard treatment for gastric cancer, and, when he was installed as President of JGCA in June 1998, he organized a committee to formulate a standard treatment for gastric cancer and took action to develop guidelines for the treatment of gastric cancer.

Current Status in Japan and Guidelines in Other Countries

At present, there are almost no systematic guidelines for cancer treatment in Japan. One outstanding exception is the guidelines for breast-conserving therapy prepared by the Japanese Breast Cancer Society. However, these guidelines are restricted to breast-conserving therapy and do not cover the treatment of breast cancer as a whole. Nevertheless, this was a pioneering attempt in the preparation of guidelines for cancer treatment in Japan.

In other countries, particularly in the U.S., various guidelines are available and open to the public. Above all, the Physicians Data Query (PDQ), a database prepared and made available through the Internet by the National Cancer Institute, lists the treatments for all types of cancer according to stage.

The PDQ is an excellent resource for several reasons. First, because it is updated at regular intervals, the literature cited is also updated frequently. Regular review of guidelines requires enormous effort, but, unless such effort is put forth, the guidelines may become more harmful than useful. Another important feature of the PDQ is that an edition of the guidelines devoid of technical terms is available to the general public, in addition to the technical
ions were held with regard to other treatments. Of course, a consensus of institutions was firm grounds for recommending a treatment as standard.

2. Principles used in formulation of the guidelines

From the results of this questionnaire survey, a symposium entitled “Establishing Treatment Standards for Gastric Cancer” was held at the 71st general meeting of JGCA in 1999. This symposium was intended to show the current status of gastric cancer treatment in Japan as it emerged from the results of the questionnaire survey. At the same time, the symposium attempted to clarify for the members of JGCA the importance of standard gastric treatment, because the significance of such treatment had not been fully comprehended, leaving room for misunderstandings to arise.

In general, doctors do not like to have restrictions placed on their treatment strategies, and they were considered likely to resist the standard treatment policies prescribed by the Association as being meaningless or even harmful and as placing restrictions on their practice of medicine. At this symposium, not only the advantages but also the possible disadvantages of developing standard treatment policies were open for discussion. As a result of the open discussion, it was pointed out that the term “standard treatment” was not appropriate, and it was changed to “guidelines” for treatment. As a consequence, doctors’ understanding and acceptance of the guidelines were greatly enhanced.

The committee then proceeded to a discussion of gastric cancer treatment including endoscopic treatments such as endoscopic mucosal resection (EMR), modified surgery, and function-conserving surgery for early gastric cancer; surgical treatment for advanced gastric cancer; and chemotherapy. Next, treatment policies were set forth as guidelines according to the stage of the disease.

In formulating the guidelines, treatments that were considered to be current standards
Based on a survey of available evidence were recommended for daily clinical practice (Table 1). On the other hand, controversial treatments were recommended for further clinical investigation (Table 2). Controversial treatments were considered to be those undergoing a process of clinical evaluation to determine their efficacy. For example, there was some controversy as to the indication of EMR for early gastric cancer; some doctors were of the opinion that it can be indicated for histologically undifferentiated cancers, whereas others disagreed. Based on its review, the committee decided that EMR for undifferentiated cancer is not a current standard because there is no clear evidence supporting this indication of EMR. This does not mean that EMR for undifferentiated cancer should be avoided. If EMR is used for undifferentiated cancer, it should be employed with well-defined indications, and the results should be reported to provide scientific evidence.

The same attitude was held toward adjuvant chemotherapy associated with surgery for gastric cancer. Although many institutions use chemotherapy for advanced cancer, there is a great deal of difference in its content, and documentation of data supporting its usefulness is insufficient. Therefore, the committee came to the conclusion that all types of adjuvant chemotherapy should be performed as part of clinical research rather than as options for daily clinical practice. It was noted that the usefulness of adjuvant chemotherapy associated with surgery should be evaluated in clinical trials in comparison with surgery without adjuvant chemotherapy. This conclusion is expected to promote clinical trials rather than to discourage them. Naturally, the guidelines would be altered if ongoing clinical trials demonstrated unequivocal results.
3. Evaluation of the guidelines

A draft of the guidelines was completed in the autumn of 1999, and was distributed to all members of JGCA. A consensus meeting then was held at the 72nd general meeting of JGCA in February 2000 in Niigata. At this meeting, committee members were to reply to criticisms presented on each aspect of the guidelines, including EMR, surgery, and chemotherapy. The hall was filled to overflowing, reflecting the strong interest of the members in the guidelines. Because of limited time, in-depth discussion of each aspect was not possible. However, opinions tended not to be critical of the guidelines themselves but were concerned more with their content. There was almost no objection to the preparation of guidelines. At that point, the committee considered the preparation of guidelines to have been approved by the members of the association, and proceeded with its elaboration of their content.

Although preparation of the guidelines was intended to be evidence-based, the possibility of bias could not be eliminated because their

Table 2  Indications of Treatments Recommended for Clinical Research According to Clinical Stage
(reproduced from “Gastric Cancer Treatment Guidelines: For Doctors,” March 2001 edition)

<table>
<thead>
<tr>
<th>Stage</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
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<tbody>
<tr>
<td>T1 (M)</td>
<td>IA</td>
<td>IB</td>
<td>II</td>
<td>IV</td>
</tr>
<tr>
<td>&gt;2.0 cm</td>
<td>EMR (fractionated resection)</td>
<td>Laparoscopic-assisted resection</td>
<td></td>
<td>Extended gastrectomy (combined resection, D3 dissection)</td>
</tr>
<tr>
<td></td>
<td>EMR→local/segmental resection</td>
<td></td>
<td></td>
<td>Volume-reduction surgery</td>
</tr>
<tr>
<td></td>
<td>Laser radiation for incomplete EMR cases</td>
<td></td>
<td></td>
<td>Chemotherapy (systemic, local)</td>
</tr>
<tr>
<td></td>
<td>Local/segmental resection</td>
<td></td>
<td></td>
<td>Hyperthermo-chemotherapy</td>
</tr>
</tbody>
</table>

T. YAMAGUCHI
preparation was entrusted to a limited number of committee members. Therefore, to determine whether any extreme bias was present, the Guidelines Review Committee, comprised of members completely different from those of the Guidelines Preparation Committee (Chair: Dr. Nakajima), was formed. The draft guidelines proposed by the preparation committee were submitted to the review committee for careful consideration, and the opinions of the review committee were then presented to the preparation committee. Based on the results of the review, the draft guidelines were again deliberated in the preparation committee, and submitted for approval by the Board of Trustees of the Association. The final proposed guidelines were distributed to all members of JGCA, and were published following the “Gastric Cancer Treatment Guidelines” forum of the 73rd general meeting of JGCA held in Kanazawa in March 2001.

Prior to publication, this set of guidelines was examined in a special program, “Consideration of Cancer Guidelines: Using the Gastric Cancer Treatment Guidelines,” of the 38th annual meeting of the Japan Society of Clinical Oncology held in October 2000. On that occasion, opinions of specialists in treating other cancers such as breast and lung cancers and those of medical journalists outside JGCA were solicited. A generally favorable evaluation of the Gastric Cancer Treatment Guidelines was obtained, and most participants were of the opinion that similar guidelines were desirable for cancers of other organs.

“Gastric Cancer Treatment Guidelines” was published by Kanehara & Co., Ltd., and is currently in its third printing. The guidelines provide an explanation of currently available treatment modalities and present them in relation to the stage of gastric cancer according to the classifications used in daily clinical practice and those used in clinical investigations. The data and documents that served as the basis for these treatment policies are also presented. Copies of the guidelines (in Japanese) are available for 800 yen each.

4. Explanation of the Gastric Cancer Treatment Guidelines: Guidelines for the General Public

Inspired by the PDQ model in the U.S., “Explanation of the Gastric Cancer Treatment Guidelines” (Guidelines for the General Public) was prepared. To obtain feedback about the “Guidelines for the General Public” in the process of preparation, the draft was distributed to the members of JGCA, together with the draft of the guidelines for doctors as a reference. In response, various comments and suggestions from the members were obtained. Comments on the draft “Guidelines for the General Public” were also collected from patients and other health care professionals such as nurses. The “Guidelines for the General Public” were published in autumn 2001 after a process of review by the review committee, in the same manner as that for the “Guidelines for Doctors,” and deliberation based on the results of such review.

In the “Guidelines for the General Public,” technical terms have been replaced by words that are easier to understand, and the stomach and stomach cancer are explained clearly using illustrations. In daily clinical practice, the “Guidelines for the General Public,” rather than those for doctors, may occupy a central role.

Critique of the Guidelines

Some doctors have expressed concern that publication of the guidelines may be associated with certain problems. Examples of their concerns include use of the guidelines to initiate medical lawsuits and possible restrictions on treatment policies that should be left to the doctors. However, doctors should abandon the idea that they can perform whatever treatment they wish simply because they have a medical license.

In regard to medical lawsuits, the guidelines may allow doctors to better fulfill their respon-
sibilities by providing clearer explanations to the patients and being able to offer them the “Guidelines for the General Public.” According to experts on similar guidelines in the U.S., lawsuits related to certain diseases have actually decreased rather than increased after the formulation of guidelines. Therefore, the doctors should assume a positive attitude with regard to use of the guidelines. To this end, the doctors should regard the guidelines as a matter of their own interest and should indicate points that need to be improved by carefully reviewing the contents of the guidelines. This process would result in better guidelines.

With regard to restrictions on treatment policies, it should be recognized that the absence of restrictions is unusual. If a doctor wishes to use a treatment other than that recommended for daily clinical practice, he or she should provide the patient with the rationale for the decision as well as information about the treatment that is considered standard. If a doctor were to perform an investigational treatment while allowing the patient to believe the treatment was commonly used in clinical practice, it could result in a lawsuit if the outcome was unfavorable. In contrast, if the doctor provided accurate information, it could lead to an increase in the number of patients wishing to participate in clinical trials, since such patients would understand the significance of the investigational treatment. Therefore, the guidelines are expected to promote rapid progress in clinical research.

The Ministry of Health, Labor and Welfare has been encouraging the preparation of guidelines for various diseases, and actually has organized investigations by various study groups. However, these governmental guidelines highlight the government’s intentions based on state interests although they may also focus on the benefits to the patients. In this regard, it seems ideal that an independent academic society, like JGCA, develops relevant guidelines independently while observing proper procedures. The preparation of this set of guidelines is of great significance in that it is independent of support from the Ministry of Health, Labor and Welfare and from health care and pharmaceutical companies. It is expected that the publication of “Gastric Cancer Treatment Guidelines” will provide an impetus for other academic societies to prepare their own guidelines.

**Future of the Guidelines: Conclusions**

The contents of the guidelines should not be preserved without alteration; rather, they should be improved by frequent reviews to reflect advances in treatment. To this end, it is essential that the doctors accumulate findings and report them accurately, and that the results of studies be evaluated fairly and rigorously by the committees, to update and improve the guidelines. Thus, the Preparation Committee and Review Committee have a great obligation to the future. There are a number of issues left untouched in the current guidelines. For example, policies in postoperative follow-up have hardly been touched. Such issues should be discussed straight away.

In April 2001, Dr. Nakajima, the chair of the Guidelines Preparation Committee, gave a special lecture, “Gastric Cancer Treatment Guidelines in Japan,” at the 4th International Gastric Cancer Congress, attracting the attention of attendees from various countries. Since a call for publication of the contents of the guidelines via the Internet was put forth by the audience, JGCA is now preparing for future publication of the guidelines in both Japanese and English at its URL. Readers of this document are encouraged to examine the “Gastric Cancer Treatment Guidelines” and submit candid comments and criticisms to JGCA.

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(website of the Japanese Gastric Cancer Association; a summary of the “Gastric Cancer Treatment Guidelines” is available at this URL.)

2) [http://cancernet.nci.nih.gov/pdq/pdq_treatment.shtml](http://cancernet.nci.nih.gov/pdq/pdq_treatment.shtml)  
(PDQ is available here.)
Is Gastric Cancer Decreasing?


Tetsuro KUBOTA

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Abstract: The incidence of gastric cancer is declining in Japan and all over the world. In a study conducted in Osaka prefecture, the age-adjusted mortality rate for gastric cancer decreased from 84 (1963–65) to 41 (1987–89) for males and from 41 to 18 for females during the same period, and the age-adjusted incidence rate also decreased from 108 (1963–65) to 68 (1987–89) for males and from 52 to 30 for females in the same period. Since a decline in gastric cancer mortality has been observed in countries where secondary prevention (screening) is not available, primary prevention is considered important in preventing gastric cancer. Several reports indicate that food type intake as a primary prevention method is important in preventing gastric cancer. Favorable food, said to prevent gastric cancer, includes green, yellow and other fresh vegetables, and milk, while salty food, stock fish, fish in salt, and too much rice are considered candidates to avoid in preventing gastric cancer. Although the decline in mortality is higher than that of incidence, almost half of the number of patients with gastric cancer in Japan are expected to die. Primary and secondary prevention, as well as advances in treatment, will be important to reduce gastric cancer mortality.

Key words: Gastric cancer; Mortality; Incidence; Primary prevention; Secondary prevention

Introduction

Incidences of gastric cancer are decreasing worldwide, and Japan is no exception. In 1998, deaths caused by gastric cancer reached 50,680, accounting for 17.9% of the mortality attributable to all types of cancers in Japan. Gastric cancer mortality has been showing a definite decrease both in males and females since around 1960.1) When changes in age-adjusted cancer mortality among the Japanese was investigated by cancer type, gastric cancer still accounted for a high percentage of mortality among females while lung cancer took the place of gastric cancer and was ranked the first in mortality among males in 1993 (Fig. 1).1) The global male/female ratio of mortality by gastric cancer is about 2.0 to 2.5, indicating a
higher rate in males, but this gender difference disappears among those under 40 years of age.

There are substantial differences between the countries in gastric cancer onset. For example, the incidence of gastric cancer among the Japanese is 7 to 8 times higher than among Caucasians in the U.S.A. In this regard, the development of prophylaxis, diagnosis, and treatment of gastric cancer in Japan, which is the only country among the developed nations to show a high incidence of this type of cancer, is considered very important from a global standpoint.

Is the incidence of gastric cancer on the decrease?

The question "is the incidence of gastric cancer on the decrease?" is a very simple one, but it is unexpectedly difficult to give an appropriate answer because there is a different nuance depending on whether the decreased figure refers to the mortality, morbidity (incidence), or the number of deaths. The most straightforward variable that shows the decrease in gastric cancer is either the mortality or morbidity. A demographic survey conducted by the Ministry of Health, Labor & Welfare discloses the former but the figures published are for mortality corrected by age and they do not necessarily indicate the number of deaths by gastric cancer. Deaths by gastric cancer among both males and females reached 31,211 in 1950 and 37,306 in 1955. The number increased, however, to reach 50,620 in 1979 and 50,076 in 1995, due to the aging of the Japanese population and an increase in the population in which the onset of gastric cancer is more common. When the incidence of gastric cancer mortality during this period is corrected to take into effect the aging of the population, the age-adjusted mortality rate decreased to 45.4 in males and 18.5 in females in 1995 as opposed to 87.3 and 48.0 respectively in 1950.

To correctly assess the yearly changes by comparing past and present increases and decreases in gastric cancer mortality, it is necessary to use the age-adjusted mortality rate calculated for each age range. The result calculated by this method clearly indicates a decrease in the mortality of gastric cancer among the Japanese (Fig. 2).

Information on morbidity can only be obtained from a population that has complete cancer records. Since December 1962, the Osaka Prefecture Medical Association, Osaka Prefectural Department of Environmental Health and Osaka Prefectural Adult-Onset Disease Center have continued to promote a project to encourage the registration of cancer.
information in Osaka Prefecture. An examination of the mortality rates by prefecture reveals that Osaka has one of the highest mortality rates among the prefectures, but its age-adjusted gastric cancer morbidity rate among both males and females has continued to decrease. While the age-adjusted morbidity in males in 1963 to 65 was 108, a decrease to 68 was observed from 1987 to 89. The morbidity in females decreased from 52 to 30 during the same period. The decrease in age-adjusted mortality was more remarkable than that of the morbidity. That is, during the same period, a decrease from 84 in 1963 to 65 to 41 in the period from 1987 to 89 was observed among males while a decrease from 41 to 18 was noted among females.

Figure 2 shows the age-adjusted gastric cancer mortality and morbidity rate estimates published by the Regional Cancer Information Registration Study Group (Chief researcher: Akira Oshima), operating under cancer research subsidies from the Ministry of Health, Labor & Welfare. The estimated gastric cancer morbidity in Japan in 1995 among both males and females was 100,842, or 2.01 times higher than 50,076, which was the number of gastric cancer deaths in the same year. Though morbidity has decreased among both males and females, gastric cancer morbidity is higher than that of lung cancer and is ranked the first among males while the morbidity in females is ranked second to breast cancer.

The decrease in gastric cancer mortality is more marked than that of morbidity. However, the decrease in morbidity itself cannot be explained by the secondary prophylaxis (diffusion of gastric cancer screening test) and improved therapeutic technology. Furthermore, the worldwide decrease in gastric cancer mortality started before 1960 — earlier than the decrease in Japan, which was noted after 1960. Decreased mortality in foreign countries where no gastric cancer screening test (secondary prophylaxis) is conducted means a decrease in morbidity, suggesting the importance of primary prophylaxis.
Decreased gastric cancer morbidity and mortality and primary prophylaxis

When macroscopically viewed, cancer morbidity and mortality trends in Japan are showing the same overall tendencies that have been observed in Europe and the United States, and incidences of gastric cancer are expected to decrease in Japan, despite the fact that Japan is the only country among the developed nations that has a high incidence of gastric cancer morbidity. Dietary changes after World War II (changes in types of foods ingested, changes in food preservation methods — salted food to refrigerated and frozen food) in particular are assumed to be involved in the lowered incidence of gastric cancer.

Factors to be avoided in the primary prophylaxis of gastric cancer are “salty food, kippered & salted fish, and a large amount of rice”. Though some case studies and cohort studies pointed out the relation between excessive intake of grain and risk of gastric cancer, there are other reports against such an assumption. Frequent large-volume grain intake is often associated with excessive ingestion of salty foods and an insufficient intake of fruits and vegetables, which all together seems to be connected with a risk of gastric cancer.

On the other hand, the factors required for prophylaxis against gastric cancer are “green and yellow vegetables, raw vegetables, and milk”. A number of case studies and cohort studies worldwide indicate that the ingestion of fruits and vegetables is effective against the onset of gastric cancer. Many studies are drawing attention to the fact that fruits and vegetables contain a large amount of trace nutrients such as vitamin C and carotenoid, which have a prophylactic effect against gastric cancer. Vitamin C is assumed to have a prophylactic effect against the onset of gastric cancer because it inhibits the generation of the carcinogenic substance, N-nitroso compound. Many case studies reported that ingesting a large amount of vitamin C inhibited the onset of gastric cancer. β-carotin is a precursor of retinol. Since retinol itself induces differentiation and demonstrates anti-tumor effects, the relation between retinol ingestion and the incidence of gastric cancer was also investigated, but a definite conclusion has yet to be reached. The prophylactic action of carotenoid and β-carotin ingestion was confirmed in many case studies. However, the effect against the onset of gastric cancer was not confirmed in a large-scale randomized intervention study of β-carotin conducted in Finland and USA. The above results indicate the possibility that green, yellow and other raw vegetables could contain factors that prevent gastric cancer other than vitamin C and carotenoid. Since gastric cancer morbidity is decreasing even in the countries where no screening is conducted, people all over the world may have come to avoid the risk factors in the natural course of time, and we can see that recent dietary changes have contributed to an automatic shift to primary prophylaxis.

Another risk factor for gastric cancer is Helicobacter pylori (“H. pylori”), which has been acknowledged a definite gastric cancer carcinogen by the U.S. FDA. It is easy to see the path from H. pylori infection to the onset of gastric cancer, through atrophy of gastric mucosa due to ammonia produced by H. pylori, to chronic gastritis, and metaplasia of intestinal epithelium and intestinal-type gastric cancer. However, the H. pylori infection rate among adults in Japan is reported to be 60 to 80%. In view of the gastric cancer morbidity of less than 100 to 100,000 (0.1%), it is difficult to assume that H. pylori fully satisfies the conditions for inducing gastric cancer. Furthermore, there is no gender difference in the H. pylori infection rate, which cannot explain why the incidence is higher in males over the world.

A number of case studies and cohort studies have indicated that smoking is a risk factor for gastric cancer. However, considering that the amount of smoking and the incidence do not always correspond, it is difficult to treat smoking as a single independent factor. On the other
hand, few case study and cohort study have indicated that alcohol intake is a risk factor for gastric cancer.

**Conclusion**

Both age-adjusted gastric cancer mortality and its estimated morbidity are on the decrease. Since this tendency is also observed in countries where no secondary prophylaxis is practiced, changes in environmental factors including dietary habits are assumed to play an important role in primary prophylaxis. A slightly higher decrease in mortality in comparison with the decrease in gastric cancer morbidity observed in Japan suggests the importance of improvements in therapeutic technology. However, mortality still accounts for about a half of morbidity, indicating that half of those who have contracted gastric cancer at present are expected to die. Gastric cancer research in Japan, which is the only developed nation to have a high incidence of gastric cancer, is considered very important from a worldwide perspective.

**REFERENCES**


Increasing Trend in the Incidence of Colorectal Cancer in Japan

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Abstract: Malignant neoplasms have been the most common cause of death among Japanese since 1981, and the number of deaths from cancers has subsequently increased at a rapid pace. In the ensuing two decades, the frequency of colorectal cancer, among other malignant neoplasms, has increased nearly two-fold, while that of gastric cancer, which was formerly higher, has diminished. In fact, the death rate for colorectal cancer (per 100,000 population) has increased 6- to 7-fold in both males and females in the past 50 years. In Japan, the five-year survival rate in curatively resected cases of colorectal cancer has improved progressively over the past 25 years or so, and therapeutic outcome in cases of advanced cancer in particular, has improved to a remarkable extent with advances in surgical techniques. Furthermore, success in detection of early carcinomas that are treatable to a complete cure has also increased markedly as the result of improved diagnostic techniques. The increased mortality of the disease despite such improvement in the cure rate reflects the fact that the incidence rate for colorectal cancer has been increasing in Japan. It is generally considered that the westernization of living environment including dietary life in Japanese society is largely responsible for this trend.

Key words: Colorectal cancer; Death rate; Incidence rate; Survival rate after curative resection; Dietary life

Introduction

Until several decades ago death rates for colorectal cancer were higher in developed western societies and lower in Southeast Asia, including Japan. In Japan, however, the incidence of this disease began rising around 1955 and this trend has subsequently continued even when viewed in terms of annual trends in mortality for the disease.

It has been shown that, even in the past when the incidence of colorectal cancer was generally thought to be lower in Japan, the morbidity rate was greater among Japanese descendants.
S. KODAIRA

...diseases has increased rapidly; 295,399 patients died of malignant neoplasms in 2000, with a death rate of 235.2 per 100,000 population, accounting for 30.7% of total deaths.

Among malignant neoplasms, high death rates were formerly recorded for gastric cancer (malignant neoplasms of the stomach), being 44.2% for men and 36.2% for women in 1970. In 2000 the death rates were 18.3% for men and 15.3% for women; hence a substantial reduction in the proportion to total deaths from all malignant neoplasms to less than half in the last three decades. In contrast, the ratio of deaths from colorectal cancer (malignant neoplasms of the large bowel) to total deaths from all malignant neoplasms increased to 11.1% for males and 13.8% for females in 2000, compared to 6.4% and 7.9%, respectively, in 1970.

In 2000, the total mortality from colorectal cancer was 19,868 men and 16,080 women; when viewed in terms of the age-adjusted death rate, colorectal cancer ranked fourth after cancer of the lung, gastric and hepatobiliary tract cancer in men, and was the second most common malignancy after gastric cancer in women.

Table 1  Trends in Death Rates (per 100,000 Population) from Malignant Neoplasm of Colon and Rectum

<table>
<thead>
<tr>
<th>Year</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950</td>
<td>1.5</td>
<td>2.0</td>
<td>2.9</td>
<td>2.5</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>1970</td>
<td>3.5</td>
<td>3.9</td>
<td>5.0</td>
<td>4.1</td>
<td>8.5</td>
<td>8.0</td>
</tr>
<tr>
<td>1980</td>
<td>6.7</td>
<td>6.9</td>
<td>6.8</td>
<td>4.9</td>
<td>13.5</td>
<td>11.9</td>
</tr>
<tr>
<td>1990</td>
<td>12.9</td>
<td>12.4</td>
<td>9.2</td>
<td>5.9</td>
<td>22.1</td>
<td>18.2</td>
</tr>
<tr>
<td>2000</td>
<td>19.8</td>
<td>18.0</td>
<td>12.6</td>
<td>7.2</td>
<td>32.4</td>
<td>25.1</td>
</tr>
</tbody>
</table>

(Vital Statistics of Japan, Statistics and Information Department, Ministry of Health and Welfare)

of immigrants in the States of Hawaii and California. Using data from animal experiments on colorectal cancer development with chemical carcinogens, it has also been demonstrated that dietary life and other life-environmental factors influence the occurrence of colorectal cancer. It is thus considered that the lower incidence of the disease in the past was not due to racial differences but to life environment, the westernization of which has led to its increase.

This paper describes the annual trends in the occurrence of colorectal cancer in Japan from various perspectives, on the basis of statistical survey data, and comments on whether the incidence of this disease has been increasing or not.

Colorectal Cancer as Viewed from Causes of Death

The average life span of Japanese was 50.06 years for males and 53.96 years for females in 1947, and had become markedly prolonged to 77.64 years for males and 84.62 years for females in 2000 according to the Vital Statistics of Japan published by the Ministry of Health, Labour and Welfare. Under these circumstances, malignant neoplasms became the most common cause of death about the beginning of 1980’s and thereafter, replacing cerebrovascular disorders which had been the most common cause until then. Since that time, the number of individuals dying from malignant neoplastic diseases has increased rapidly; 295,399 patients died of malignant neoplasms in 2000, with a death rate of 235.2 per 100,000 population, accounting for 30.7% of total deaths.

Among malignant neoplasms, high death rates were formerly recorded for gastric cancer (malignant neoplasms of the stomach), being 44.2% for men and 36.2% for women in 1970. In 2000 the death rates were 18.3% for men and 15.3% for women; hence a substantial reduction in the proportion to total deaths from all malignant neoplasms to less than half in the last three decades. In contrast, the ratio of deaths from colorectal cancer (malignant neoplasms of the large bowel) to total deaths from all malignant neoplasms increased to 11.1% for males and 13.8% for females in 2000, compared to 6.4% and 7.9%, respectively, in 1970.

In 2000, the total mortality from colorectal cancer was 19,868 men and 16,080 women; when viewed in terms of the age-adjusted death rate, colorectal cancer ranked fourth after cancer of the lung, gastric and hepatobiliary tract cancer in men, and was the second most common malignancy after gastric cancer in women.

Annual Trends in Death Rates for Colorectal Cancer

According to the Vital Statistics of Japan, the death rate (per 100,000 population) for
colorectal cancer was 4.5 for both men and women in 1950 and increased year on year to 13.5 for men and 11.9 for women in 1980 and to 32.4 and 25.1, respectively, in 2000 as seen in Table 1. Thus, there were 7.2-fold and 5.6-fold increases for males and females, respectively, as compared to the rates 50 years ago, and the increases were 2.4-fold for men and 2.1-fold for women, compared to those 20 years previously (1980).

With the carcinomas of the large bowel being classified into cancer of the colon and cancer of the rectum, the death rate for both cancers has increased progressively in both genders although the increase has been more conspicuous for cancer of the colon.

Changes in the Frequency of Colorectal Cancer by Tumor Location

The total number of cases of colorectal cancer is on the increase. As for frequencies of colorectal cancer by tumor location according to the Multi-Institutional Registry of Large Bowel Cancer in Japan issued by the Japan Society for Cancer of the Colon and Rectum (JSCCR), as shown in Fig. 1, rectal carcinomas accounted for more than half (55.9%) of all cases of colorectal cancer in the mid 1970's. The frequency of cancer of the rectum gradually declined thereafter, dropping to less than 50% in 1985, and further to 40% in 1997, this being the latest statistical data. The frequency of cancer of the colon, in contrast, has shown a tendency to increase for all sites of involvement. Currently, a marked increase in the incidence of carcinomas of the cecum and ascending colon, i.e., carcinomas of the right colon, is noteworthy while cancer of the sigmoid colon makes up about one-fourth (25.6%) of all cancers of the large bowel.

Notwithstanding the decline in the incidence of cancer of the rectum, the anorectal canal accounts for approximately 10% of the whole length of large bowel and nearly 40% of all colorectal carcinomas occur in that region. This region thus remains a site with a greater risk for cancer development than other regions.
Changes in Survival Rates for Cases with Curative Resection

In estimating the incidence rate from the death rate for colorectal cancer, it is important to clarify the percentage of patients with colorectal cancer in whom a complete cure is attained by treatment.

In terms of changes in five-year survival rates after curative resection of colorectal cancer (adenocarcinoma alone) in Japan since the Multi-Institutional Registry of Large Bowel Cancer in Japan was initiated in 1974, the overall five-year survival rate for curative resection cases of colorectal cancer was 71.1% for cancer of the colon and 57.7% for cancer of the rectum in 1974–1975. The outcome then improved year on year to become 83.9% and 79.8%, respectively, in 1994 according to the latest data; hence a remarkable improvement for both cancer of the colon and that of the rectum (Table 2).

The five-year survival rate by stages of carcinoma (Dukes staging) improved noticeably in cases of Dukes B or C disease, and the five-year survival rate for rectal carcinoma in particular, improved by more than 20% in 15 years in cases of Dukes B or C disease. This is considered to be largely attributable to the elucidation of the disease state of large bowel carcinoma, advances in surgical techniques, and development of surgical adjuvant chemotherapy. However, it should be pointed out that the increased opportunity for early detection of colorectal cancer as a result of the increased prevalence of examinations such as fecal occult blood tests and improved diagnostic techniques, has also contributed to the overall improvement in the five-year survival rate.

Colorectal Cancer Is Increasing in Japan

There are no exact figures for cases with colorectal cancer in Japan because no complete surveys have been conducted as to the actual state of the incidence rate. The numbers of patients dying as a result of cancer of the large bowel and the death rates (per 100,000 population) for the disease have increased 6- to 7-fold for both genders in the past five decades or so, as described above. There have been significant improvements in the therapeutic outcome in cases of colorectal cancer, especially of advanced carcinomas, and improved diagnostic techniques have led to the detection and treatment of a considerable number of cases of early carcinoma for which the cure rate is close to 100%. Under these circumstances, the fact that the number of patients dying from large bowel carcinoma has actually been increasing may well be construed as implying that the number

<table>
<thead>
<tr>
<th>Year (No. of cases)</th>
<th>overall</th>
<th>Dukes A</th>
<th>Dukes B</th>
<th>Dukes C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer of colon</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1974·1975 (734)</td>
<td>71.1%</td>
<td>88.0%</td>
<td>73.0%</td>
<td>57.3%</td>
</tr>
<tr>
<td>1980·1981 (1,766)</td>
<td>72.3</td>
<td>82.5</td>
<td>75.7</td>
<td>63.6</td>
</tr>
<tr>
<td>1985 (1,576)</td>
<td>76.9</td>
<td>90.6</td>
<td>79.6</td>
<td>65.8</td>
</tr>
<tr>
<td>1994 (2,262)</td>
<td>83.9</td>
<td>93.4</td>
<td>84.5</td>
<td>74.0</td>
</tr>
<tr>
<td>Cancer of rectum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1974·1975 (1,015)</td>
<td>57.7%</td>
<td>78.2%</td>
<td>58.6%</td>
<td>42.7%</td>
</tr>
<tr>
<td>1980·1981 (2,033)</td>
<td>65.6</td>
<td>85.8</td>
<td>69.1</td>
<td>48.2</td>
</tr>
<tr>
<td>1985 (1,528)</td>
<td>70.1</td>
<td>84.9</td>
<td>74.6</td>
<td>52.9</td>
</tr>
<tr>
<td>1994 (1,517)</td>
<td>79.8</td>
<td>93.9</td>
<td>79.8</td>
<td>64.7</td>
</tr>
</tbody>
</table>

(from Multi-Institutional Registry of Large Bowel Cancer in Japan)
INCIDENCE OF COLORECTAL CANCER IN JAPAN

Table 3  Annual Trends in Energy Intake by Nutrients

<table>
<thead>
<tr>
<th>Year</th>
<th>Total energy</th>
<th>Protein</th>
<th>Fat</th>
<th>Carbohydrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>2,096 kcal</td>
<td>13.3%</td>
<td>10.6%</td>
<td>76.1%</td>
</tr>
<tr>
<td>1965</td>
<td>2,184</td>
<td>13.1%</td>
<td>14.8%</td>
<td>72.1%</td>
</tr>
<tr>
<td>1970</td>
<td>2,210</td>
<td>14.0%</td>
<td>18.9%</td>
<td>67.1%</td>
</tr>
<tr>
<td>1975</td>
<td>2,268</td>
<td>14.6%</td>
<td>22.3%</td>
<td>63.1%</td>
</tr>
<tr>
<td>1980</td>
<td>2,119</td>
<td>14.9%</td>
<td>23.6%</td>
<td>61.5%</td>
</tr>
<tr>
<td>1985</td>
<td>2,088</td>
<td>15.1%</td>
<td>24.5%</td>
<td>60.4%</td>
</tr>
<tr>
<td>1990</td>
<td>2,026</td>
<td>15.5%</td>
<td>25.3%</td>
<td>59.2%</td>
</tr>
<tr>
<td>1993</td>
<td>2,034</td>
<td>15.6%</td>
<td>25.7%</td>
<td>58.7%</td>
</tr>
</tbody>
</table>

Source: National Nutrition Survey by the Ministry of Health and Welfare

Table 4  Annual Trends in Food Intake by Foodstuff Categories

<table>
<thead>
<tr>
<th>Year</th>
<th>Total amount</th>
<th>Grains</th>
<th>Potatoes &amp; taro</th>
<th>Beans</th>
<th>Green &amp; yellow vegetables</th>
<th>Fish</th>
<th>Meat, including chicken</th>
<th>Dairy products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>1,128 g</td>
<td>452.6 g</td>
<td>64.4 g</td>
<td>71.2 g</td>
<td>39.0 g</td>
<td>76.9 g</td>
<td>18.7 g</td>
<td>29.5 g</td>
</tr>
<tr>
<td>1965</td>
<td>1,161</td>
<td>418.5</td>
<td>41.9</td>
<td>69.6</td>
<td>49.0</td>
<td>76.3</td>
<td>29.5</td>
<td>48.8</td>
</tr>
<tr>
<td>1970</td>
<td>1,271</td>
<td>374.1</td>
<td>37.8</td>
<td>71.2</td>
<td>50.2</td>
<td>87.4</td>
<td>42.5</td>
<td>68.4</td>
</tr>
<tr>
<td>1975</td>
<td>1,412</td>
<td>340.0</td>
<td>60.9</td>
<td>70.0</td>
<td>48.2</td>
<td>94.0</td>
<td>64.2</td>
<td>98.4</td>
</tr>
<tr>
<td>1980</td>
<td>1,352</td>
<td>319.1</td>
<td>63.4</td>
<td>65.4</td>
<td>51.0</td>
<td>92.5</td>
<td>67.9</td>
<td>107.8</td>
</tr>
<tr>
<td>1985</td>
<td>1,346</td>
<td>308.9</td>
<td>63.2</td>
<td>66.6</td>
<td>73.9</td>
<td>90.0</td>
<td>71.7</td>
<td>108.0</td>
</tr>
<tr>
<td>1990</td>
<td>1,323</td>
<td>282.7</td>
<td>65.3</td>
<td>68.5</td>
<td>77.2</td>
<td>95.3</td>
<td>71.2</td>
<td>130.1</td>
</tr>
<tr>
<td>1993</td>
<td>1,328</td>
<td>282.3</td>
<td>62.5</td>
<td>65.9</td>
<td>81.6</td>
<td>96.2</td>
<td>73.7</td>
<td>130.8</td>
</tr>
</tbody>
</table>

Source: National Nutrition Survey by the Ministry of Health and Welfare

of patients with this disease is increasing. Colorectal cancer is still on the increase in Japan.

Changes in Dietary Life

To date, it has been demonstrated that APC, K-ras, p53, MCC, and mutations of many other cancer-associated genes are involved in the carcinogenic process of colorectal cancer, but the precise causes for such changes remain to be clarified. Regarding the etiology of cancer of the large bowel, however, the following have been indicated to have bearing on the increase in the frequency of colorectal cancer, based on various epidemiologic investigations and experimental studies: increased secretion of bile acids, especially of secondary bile acids, due to a high-fat diet, and production of carcinogens through the metabolic process of bile acids, e.g., due to altered enteric bacterial flora; increased concentrations of carcinogenic substances in feces which are concentrated as a result of a low-fiber diet; a prolonged transit of the intestinal contents with a consequent extension of the contact time of carcinogens with the intestinal mucosa; and so forth.

Regarding the changes in dietary life in postwar Japan, annual trends in energy intake by nutrients presented in the National Nutrition Survey by the Ministry of Health and Welfare reveal that protein intake, which was 13.3% in 1960, has not changed appreciably (15.6% in 1993) and that carbohydrate intake decreased markedly from 76.1% in 1960 to 58.7% in 1993, while fat intake increased noticeably from 10.6% to 25.7% (Table 3). Furthermore, the proportion of animal fat in total fat intake has
increased. According to the annual trends in dietary intake by food categories presented in the Survey, the intake of grains has decreased substantially while an increase of close to 4 fold was observed for meat (including chicken) and dairy products in 1993 as against intake in 1960 (Table 4).

Such westernization of dietary life, that is, increased intakes of animal fat and protein and decreased edible fiber intake, is considered to be chiefly responsible for the increase in the incidence of colorectal cancer in Japan.

**Prevention of Colorectal Cancer**

Measures against the increase of colorectal cancer in Japan, that is, prevention of the disease, include primary prevention to ward off the development of carcinoma of the large bowel and secondary prevention to prevent fatality from cancer of the colon and/or rectum via early detection of the carcinoma and early institution of treatment.

Primary prevention, as described above, includes committing to a well-balanced diet and maintenance of a regular bowel habit by avoiding high-fat meals (particularly animal fat), taking at least 20–25 g of edible fibers daily, and ingesting vitamins C, E, and A which are thought to be useful in the suppression of formation and detoxification of carcinogenic substances.

A more realistic method of preventing colorectal cancer is secondary prevention. Detection and treatment of an early cancerous state and treatment of adenoma being regarded as a precancerous lesion by augmenting and improving the examination system including stool occult blood tests and periodic examination of the large bowel such as in a complete medical checkup are considered to be important aspects of treatment.

**Conclusion**

The incidence rate for colorectal cancer has definitely been increasing in Japan when viewed from various perspectives, and it would seem that cancers of the colon, especially those in the right-side colon, rather than of the rectum have increased. In order to further suppress the death rate for colorectal cancer, it is fervently hoped that primary prevention of the disease, to say nothing of the importance of secondary prevention, will become feasible through further pursuit of research on carcinogenetic mechanisms.

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Pathogenesis and Treatment of Ulcerative Colitis

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Abstract: In patients with ulcerative colitis, chronic inflammation sometimes persists even during remission periods, with infiltration of lymphocytes into the mucosa of the colon. When the disease becomes active, infiltration of the colonic mucosa by neutrophils and monocytes or macrophages, as well as numerous T cells or IgG containing cells, becomes prominent and this leads to mucosal injury. The pathology of this condition mainly involves abnormalities in the production of cytokines and the production of autoantibodies, as well as an abnormal responses of T cells to antigens in the intestine. These pathological features are associated with aberrant maturation and functioning of lymphocytes and colonic epithelial cells. To achieve remission, corticosteroids are commonly used. However, steroids are only effective for short-term induction therapy and their efficacy in maintaining remission has not been demonstrated. Immunomodulatory therapy is one of the new therapeutic modalities for the treatment of ulcerative colitis. Immunosuppressants such as azathioprine, 6-mercaptopurine, cyclosporine, and tacrolimus have been used for this purpose. In Japan, leukocytapheresis is also commonly used, as well as drugs described above, while probiotics (intestinal bacterial preparations) may be able to correct local immune abnormalities in the intestinal mucosa and seem to be promising immunomodulators.

Key words: Ulcerative colitis; Autoantibodies; Cytokines; Immunosuppressants

Introduction

Ulcerative colitis (UC) is an inflammatory disease of the colon with an unknown etiology, which clinically manifests with rectal bleeding, diarrhea, abdominal pain, and weight loss. The disease is both acute and chronic. The lesions are limited to the colon and extend proximally from the rectal mucosa to involve varying portions of the colon, but there are some systemic...
complications. Various theories have been proposed about its pathogenesis, including viral and bacterial infection, autoimmunity, and vascular injury. Major advances in molecular biology have led to various important findings, but its etiology and pathogenesis are still not definitively understood. Like many other autoimmune disorders, UC seems to result from complex interactions of the immune system, since the peak age of onset is around 20 years, certain autoantibodies have been detected in the serum of some patients, and it is associated with various autoimmune diseases.

A number of genetically engineered animal models of intestinal inflammation have recently been described and extensively reviewed. Understanding the disease mechanism of these models should be useful for clarifying the immunological abnormalities of UC. Animal models, such as IL-2, IL-10, and TCR α/β knockout mice, do not develop colitis in a germ-free environment. This suggests that an environmental factor, such as nonpathogenic microorganisms present in the enteric flora, as well as host immune abnormalities caused by genetic factors, induce and maintain mucosal inflammation in these models.

Chronic hepatitis may be induced by various causes, including hepatitis B/C virus infection and autoimmunity. Likewise, the significant progress made during the past decade has led to the realization that UC probably also develops from multiple causative factors.

**Pathogenesis of UC**

1. **Antibodies and B cells**

   The pathophysiology of UC is shown in Fig. 1. An increase of lymphocytes, especially activated T cells and IgG-containing B cells, is seen in the colonic mucosa. This may induce the increased production of antibodies directed against intestinal antigens and autoantigens. In addition, a role of the type I allergic response has been suggested in the development of acute exacerbation. Autoantibodies, such as anti-colon antibody and anti-neutrophil cytoplasmic antibody (ANCA), are detected in the serum.
of some UC patients and damage to the colonic mucosa is assumed to be due to antibody-dependent cell-mediated cytotoxicity (ADCC) involving these autoantibodies. In other words, a functional abnormality of mucosal T cells and associated activation of antibody-producing cells seems to promote the local production of autoantibodies in the colonic mucosa that may contribute to the pathogenesis of this disease. However, these antibodies are not present in all patients and there is no correlation between such antibodies and disease activity or the duration of illness. Thus, it is possible that these antibodies may develop secondary to inflammation without any pathogenic activity. At the present time, therefore, there is not enough evidence about the role of autoimmunity in UC.

2. Cytokines and T cells

In the normal state, the mucosal immune system is involved in the suppression or inhibition of immune responses to the intestinal contents. The concept that this tightly regulated state is altered in UC has been proposed by many groups. Various abnormalities of the cytokine network occur in the colonic mucosa of UC patients, resulting in uncontrolled and sustained inflammation. We have focused on defective regulation of the differentiation and proliferation of the thymic T cell lineage in UC patients and have described a factor that affects the processing of thymic T cells. Purification of this factor revealed that it was IL-7. Because IL-7 produced by intestinal epithelial cells regulates the proliferation of mucosal T cells, disruption of this mechanism could lead to abnormal perpetuation of inflammation. There is considerable evidence that defective mucosal immunoregulation, including abnormal changes of T cells, B cells, granulocytes, mac-
rophages, and the cytokines and chemokines produced by these cells, plays a major role in the pathogenesis of UC. The current need is to clarify the factor(s) that lead to defective immunoregulation.

Treatment

The etiology of UC is unknown and the need to rely upon empirical therapies is disquieting. Therapeutic options can be divided into those that attempt to modify the presumed etiopathogenesis of UC and those that attempt to control the symptoms. Most patients with UC experience relapse and disease progression during their clinical course. Therapy for UC has been categorized an induction therapy, maintenance therapy, treatment for refractory disease, and surgery. Efficacious acute therapy and safe maintenance therapy are essential for the medical treatment of UC. Physicians should treat patients according to the revised guidelines prepared by the Ministry of Health and Welfare disease study group in 1998, taking into account the severity, extent, and type of disease in individual cases.

Aminosalicylate preparations (5-ASA), corticosteroids, and immunomodulators are the three main classes of agents used in the medical treatment of UC. Antispasmodics (primarily anticholinergic agents) and antidiarrheal preparations are recommended to improve the symptoms that accompany UC. There is no routine role for sedatives, antidepressants, or antipsychotic therapy, but, low doses of antidepressants are occasionally employed to ameliorate IBS symptoms in patients with UC.

1. 5-ASA preparations

Sulfasalazine, the prototype aminosalicylate formulation, was initially developed with the concept of delivering both an antibacterial agent (sulfapyridine) and an anti-inflammatory agent (5-aminosalicylic acid, mesalamine, mesalazine) to the connective tissues. Although it remains the benchmark agent, recognition that the 5-aminosalicylic acid moiety is the major source of therapeutic benefit and that sulfapyridine is responsible for most of the side effects has encouraged the development of a series of sulfa-free aminosalicylates. 5-ASA drugs are now available in a variety of formulations, and these agents are efficacious in the treatment of UC as long as the active component (5-ASA) is delivered to the site of disease activity. Pentasa is a recently developed sustained-release preparation (coated with ethylcellulose) that delivers 5-ASA to the distal ileum and colon. The incidence of side effects is less than half of that reported for sulfapyridine, but some patients may experience similar side effects with either drug. Worsening of diarrhea and high-grade fever without evidence of severe disease activity are indications for discontinuing this drug.

For induction of remission, oral sulfasalazine at doses between 3 and 4.5 g daily is recommended. Pentasa (1.5 to 2.25 g/day orally) is used for the same purpose, but doses of up to 3 or 4 g/day are recommended in Western countries. The suggested maintenance dose of sulfasalazine is between 2 and 3 g daily, while it is 1.5 to 2.25 g for Pentasa. The need for continuing maintenance therapy remains controversial. Although continuation of daily therapy is optimal from the standpoint of efficacy, discontinuation of aminosalicylates is possible if the patient has been in remission for two to three years.

2. Corticosteroids

Corticosteroids are the most commonly used agents for the treatment of UC patients with moderate to severe activity. The glucocorticoids have an effect on many aspects of the immune and inflammatory responses. Oral or parenteral corticosteroids are indicated for the treatment of ambulatory patients with moderate to severe colitis whose symptoms cannot be controlled by aminosalicylates. Topical steroids, including suppositories, foams, and enemas, have a definite role in the treatment of distal
colitis. Moderate colitis requires treatment using a system corticosteroid combined with an aminosalicylate. Ambulatory patients are usually treated with prednisolone and the starting dose is between 30 to 60 mg/day. This dose is gradually tapered until the patient is passing normal bowel movements without blood or urgency. If symptoms improve rapidly, the dose of prednisolone can be tapered by 5 to 10 mg/week. Patients who are slower to respond require a more gradual tapering schedule, but continuation of high-dose prednisolone must be avoided. If tapering of steroids seems to be difficult, alternative therapy must be taken into consideration. Patients with severe or fulminating colitis require hospitalization and parenteral steroids. Autely ill patients can be treated with high doses of intravenous corticosteroids for 3 to 5 days, such as methylprednisolone pulse therapy. Mesenteric artery infusion of corticosteroids is effective for some patients, but consultation with a surgeon about colectomy is necessary in such cases.

3. Immunomodulators

In the majority of patients, remission is obtained with aminosalicylates and corticosteroids. If it is impossible to taper corticosteroids or frequent relapses occur, immunomodulating therapy should be considered. However, the use of immunomodulators is not approved by the national health insurance scheme, so Japanese physicians are not so experienced with these agents. There are still some specialists who affirm that immunomodulators are ineffective for the treatment of UC while causing serious toxicities. Our experience shows that administration of low-dose azathioprine or 6-MP is beneficial for steroid-dependent UC, but it requires several months for improvement to occur. Reduction of the dose of steroids or even discontinuation may be possible without relapse. Randomized controlled clinical trials have shown strong evidence for the efficacy of these drugs, and they are widely used in Western countries. The major side effects of azathioprine and 6-MP are myelosuppression (leukopenia), nausea, pancreatitis, and opportunistic infection. However, these problems are not so common with the doses currently used for IBD. Overall, there has been increasing acceptance of the use of immunosuppressants to treat IBD based on their clinical utility and low toxicity.

With an increasing number of women developing UC during their reproductive years, questions now are frequently asked regarding the effect of pregnancy and delivery on UC. The incidence of congenital abnormalities, spontaneous abortions, and stillbirths is similar for patients in remission and the general population. Several studies have demonstrated that pregnancy has no significant effect on the course of IBD and the use of any medication during pregnancy remains a controversial issue. 5-ASA drugs and corticosteroids have been demonstrated to be safe during pregnancy and the postpartum period. In addition, there have been no reported fetal abnormalities after treatment with 5-ASA drugs and corticosteroids at doses of 30 mg or less (as prednisone). However, there still is a paucity of safety data about the use of immunosuppressive agents during pregnancy. Discontinuation of azathioprine/6-MP is recommended during pregnancy and breast-feeding because there are no safety data to support their use. With good control of disease activity, the UC patient will have the same chance to conceive as someone without UC.

In addition to medical treatment, lifestyle guidance is also important. Patients should lead a regular life and obtain sufficient sleep. An unbalanced diet and drinking much alcohol should be avoided. It is important to explain the basic pathophysiology to the patients and their families, so that they may at least keep the minimum requirements.

4. Novel therapies

The standard therapeutic modalities have been described above. Leukocyte apheresis and the introduction of cyclosporine have been the
most dramatic changes in the past few years. Both therapies are used in steroid-resistant cases. Leukocyte apheresis is a treatment in which lymphocytes and granulocytes are removed by adsorption or rapid sedimentation once or twice a week. Until now, its efficacy has only been reported in Japan. The Adacolumn®, which selectively removes granulocytes from the peripheral blood, has been approved by the Japanese health insurance scheme since April 2000. However, for the time being, it can only be used in special facilities.

Intravenous cyclosporine seems to be beneficial for the management of severe, refractory UC. Its efficacy has been supported by a number of clinical studies in Western countries, but its application in Japan is still uncommon, and the need for strict monitoring of blood levels and potential side effects limits its use to special facilities. Various new treatments are currently being tested, and as more effective medical therapy is established more patients are being treated for longer periods without surgery.

5. Indications for surgery

Massive hemorrhage, perforation, and fulminant toxic colitis are indications for surgery. Failure of medical therapy to control symptoms of UC and development of cancer are common indications for surgery. In UC patients total colectomy, removal of the entire colonic and rectal mucosa is curative. At present, restorative proctocolectomy with ileal pouch-anal anastomosis with the goal of total mucosal removal and maintains gastrointestinal continuity. In the absence of acute complications or carcinoma, the patient initially is treated with medical therapy. When medical therapy fails to alleviate symptoms or produces unacceptable side effects, or a complication arises, surgical treatment is required. However, it is premature to abandon medical therapy, including corticosteroids, and assume that it has failed before it has been optimally applied. A gastroenterologist must be consulted before the decision to operate is confirmed.

Conclusion

The recently available treatment options are summarized in Table 1. However, the new therapies, as well as the conventional therapies, are noncurative. Continued extensive investigation of the cause of the intestinal inflammatory response may yet transform UC from a treatable to curable disease. Patients require reassurance that, despite the absence of a known cause, medical therapy usually is effective and the quality of life is preserved. It is imperative to comprehend perspectives and concerns of the patient and family members who are confronted with a chronic, socially embarrassing, and potentially disfiguring condition. The physician must be a source of quality medical care, information, and support regarding the disease, in addition to coordinating ancillary care and professional consultation as needed to manage the patient and reassure the family over the years.

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<td>Non-pathogenic E. coli, Immune milk</td>
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**Home Medical Care and Treatment of Decubitus (Bedsores)**


Izumi YAMAMOTO

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**Abstract:** As society ages, large numbers of decubitus patients are being treated at home. Tokyo clinical dermatologist’s association offers a “110 Bedsores” emergency line, and the number of house calls made by dermatologists is rising. Important causes of decubitus are, locally, continuous pressure and, systemically, nutriture and posture adjustment handicaps. Decubitus is ranked from 1 to 4 depending on their depth, and deep decubitus is grouped into a black phase, yellow phase, red phase or white phase on the basis of their progress. Decubitus requires treatment that corresponds to progress and condition. The basic local management is to avoid pressure. And as adequate posture adjustment is often difficult in home nursing, it is important to make early use of air mattresses or other pressure relieving devices. If a black-phase decubitus is subject to vibration, an early house call is required to perform incision or debridement. The ulcerated area should be washed with physiological saline, and external medicine be applied depending on the state of the decubitus. Systemically, it is important to maintain nutriture and the movements of routine activities. Home care and treatment require a concerted effort on the part of the doctor, family, visiting nurses, and care workers.

**Key words:** Decubitus; Home care; “110 Bedsores”; Classification of decubitus by color

**Introduction**

Home care of the bedridden elderly is now regarded highly important as society ages and the long-term care insurance system has been implemented. Decubitus is quick to develop in the bedridden elderly, and many decubitus patients are treated at home. In this article home care and treatment of decubitus will be discussed.

The home treatment of decubitus requires cooperation of a dermatologist with extensive experience in treating decubitus. The Tokyo Clinical Dermatologist’s Association provides an emergency telephone service called “110 Bedsores” that responds to calls and recom-
mends nearby dermatologists who can make house calls to treat decubitus and other dermopathies. More and more dermatologists are making house calls, not only in Tokyo but all around the country, making it possible for patients and caretakers to obtain the cooperation of dermatology specialists in treating decubitus.

Factors in the Onset of Decubitus

Decubitus is a cutaneous and subcutaneous tissue lesion that lapse into irreversible necrosis due to continuous pressure on a part of the body incapable of spontaneous motor activity causing the obstruction of blood circulation.

There are local factors and systemic factors behind the onset of decubitus \(^2\) (Fig. 1).

Among the major local factors the first is pressure, the second, friction and slippage, and the third, dampness from the incontinence of feces and urine. The most important of these is local, continuous pressure; continuous pressure of 200 mmHg for two hours or more leads to local necrosis. Loci of bone protrusions are especially susceptible to local pressure and, since they have little muscular or subcutaneous tissue, to blockage of blood flow.

The favorite site of decubitus is the sacral region, accounting for over 50% of instances, followed by the leg joints and the greater trochanter. Decubitus may also develop in the coccygeal region due to drag on the skin when raising the bed. Decubitus also readily develops in the ischiatic region when seated for long periods of time.

Systemic factors include 1) impaired consciousness, 2) nutriture, and 3) posture adjustment handicaps (bedridden conditions). Statistically cases of cerebro-vascular accidents, Parkinsonian syndrome, spinal neuropathy, and cranial neuropathy are common basic illnesses underlying decubitus.

Among nutriture conditions, hypoalbuminin...
Anaemia and anaemia reduce endurance of tissue. At least 3.5 g/dl of albumin and 11 g/dl of haemoglobin are considered desirable for preventing and treating decubitus.

As the number of elderly bedridden by such causes as cerebro-vascular accidents, broken bones, senility is rising, in order to prevent disuse atrophy it is necessary to provide guidance to help them out of bed as much as possible in their daily routine and to have them maintain and upgrade the activities of daily living (ADL).

The infection of a decubitus is another important factor as it may induce other infectious diseases such as cellulitis, pneumonia, and urinary tract infection.

The Severity of Decubitus and the Course of Their Symptoms

Many factors are involved in the evaluation of the severity of decubitus such as their size, depth, infection, and surface attributes, but they are generally classified according to depth, and Shea’s system of classification is often used.

The first level is an acute inflammation generalized across soft tissue. Lesions are confined to the epidermis, and epidermal erosion may be observed.

The second level is an ulcer generalized across all dermal layers accompanying general inflammation of soft tissue.

The third level is a deep ulcer extending from subcutaneous tissue to the fascia.

The fourth level is lesions throughout all layers of the fascia and soft tissue extending to bone and articulars, and exhibiting exposure of bone.

Deep, pocket-shaped ulcers are also noted for their occlusion.

Decubitus of the first and the second level of severity is considered shallow, and the third and the fourth levels considered deep, the distinction being drawn at the fascia.

Deep decubitus takes a chronic course, and its surface attributes change in accordance with that course. The system of decubitus classification according to color proposed by Fukui usefully describes the course of chronic deep decubitus lesions. Decubitus develops through black, yellow, red, and white phases.

In the black phase, the surface of a decubitus is covered by blackish-brown necrotic tissue, accompanied by flaring and swelling at its circumference. A purulent effusion pools immediately beneath the necrotic tissue. These black-phase lesions require surgical treatment by a physician, and it is essential for the home care patient to receive a house call.

In the yellow phase, yellow presents in the ischemic granulation around the necrotic tissue, and may present as yellowish-brown or yellowish-green if contaminated by bacteria. Since the wounds are easily infected at this stage, the necrotic tissue must be removed and the affected area washed.

In the red phase, extensive and benign granulated tissue develops to cover the capillary vessels. The wounds gradually become shallow, and epithelization begins around their borders.

In the white phase, the granulated tissue contracts, there is epithelization around the circumference, and the wounds begin to scar and heal.

Home Care and Treatment of Decubitus

1. Local management of decubitus

The first necessary local management to prevent the onset and aggravation of decubitus is to avoid pressure.

Indices such as the Braden Scale and K Scale are used to evaluate the risk of onset of decubitus. Pressure relieving devices are used where it is deemed that decubitus may develop readily. If a decubitus is already present, use of a pressure relieving device is the basis of treatment to prevent its aggravation and relapse.
A change of posture every two hours is indeed effective in the prevention and treatment of decubitus, but home care places a large burden on the caregiver and changes of posture are especially difficult at nighttime. It is better to use an appropriate pressure relieving device at an early stage, which would allow the number of times of posture changing be kept to a minimum.

The patient should be provided with an air mattress for pressure relief as early as possible. Pressure-switching air mattresses are effective, and those that generate waves or alternate inflation are recommended. The air pressure of an air mattress is adjusted on a body weight scale, but the caregiver must also insert a hand beneath the mattress directly to make sure there is sufficient air so that the patient’s body does not touch the bottom side. When seated in a chair or wheelchair, the patient requires a cushion, and it is preferable to use a high-density urethane foam cushion for wheelchairs. Where contracture is an issue, interposition of a pillow or cushion will serve to relieve pressure. The caregiver must also watch for contact with urination tubes and bed fencing.

2. Local intervention for decubitus

The acute phase of a deep decubitus requires incision and drainage or debridement. In case of contact with wave motion in the black phase, an early house call is required to perform incision. Gradual debridement of the ischemic granulation is called for in the yellow phase. Isodin® may be used for disinfection, but it should be restricted to the circumference of wounds and physiological saline used to wash the ulcer. To wash the ulcer, a 23-gauge needle is used to open a hole in a plastic tube with 20 ml of physiological saline which will spurt from the hole. A 100 ml bottle of physiological saline pierced with an 18–22 gage needle may also be used.

Appropriate external medicines for the black and yellow phases are the antibacterial U-PASTA® and Geben® cream. If parts remain infected in the red phase, they are treated in the same way as during the yellow phase. If benign granulation is observed during the red phase and there are no signs of infection, one can switch to such external medicines as Olcenon® ointment, Actosin® ointment or Prostandin® ointment that promote the formation of granulation so that the period of treatment be shortened. The recently marketed Fiblast Spray® may also be used for treatment during the red phase.

Hydrocolloids and other similar medicinal patches are used for decubitus of second-level depth or shallower. Since decubitus infections may be overlooked at home, medicinal patches should not be used on decubitus of third-level depth and deeper. Irregular gel hydrocolloids such as Granugel® are also used for deep decubitus.

To treat bacterial infections of decubitus, an attempt can be made to culture the bacteria in the pus or on the surface of the ulcer and classify the pathogen, but it is also effective to presume the pathogen immediately on the basis of odor and color of stain on gauze, and to start treatment accordingly at an early stage. In treating a decubitus infection, it is necessary not only to make local use of antibacterial agents, but also to perform systemic administration of the appropriate antibiotics. If the infection is grave, hospitalization should be considered.

The most important objectives of home care and treatment of decubitus are to get through the black and yellow phases as quickly as possible and to proceed to benign granulation without infection in the red phase.

3. Skin care for decubitus patients

Caregivers should refrain from bathing a decubitus patient when there are symptoms of severe inflammation and pus discharge, but in so far as the systemic condition otherwise allows, caregivers should bathe patients proactively. When a patient cannot be bathed, they should be bed-bathed, their genital area
washed, and the affected area kept clean. When
the affected area is susceptible to dampness
due to urinary incontinence, care should
include white vaseline or a moisture-retaining
external medicine around the affected area,
spraying the area with the commercial wipe
Sanina® and care of the skin.

4. Systemic management of decubitus patients
Since there is often little hope for improve-
ment in the basic illness rendering an elderly
patient bedridden, what is important is to work
to maintain and improve their remaining activi-
ties of daily living (ADL).

Patients who are not yet bedridden must not
be left in bed, but managed to prevent disuse
atrophy.

Meals and nutrient supplements should be
designed for sufficient ingestion of nutrients.
Minimum targets are 3.5 g/dl of albumin and
11g/dl haemoglobin. When a patient is not
taking enough food, Ensure Liquid® solution
or the like may be prescribed to supplement
nutrition. Attention to infections other than
decubitus infections is required.

Cooperation with Medical Caregivers
in the Home

Home care and the treatment of decubitus
requires the close cooperation of everyone
involved, including caregivers. Home care and
the treatment of decubitus involve a large
number of care giving members: the attending
physician, a dermatologist, the patient’s family,
visiting nurses, home helpers, visiting bath
attendants, care welfare workers, and care
managers.

When making house calls, a physician must
give the patient’s family and visiting nurses
instructions how to change dressings daily and
how to administer external treatment, and
house calls must be coordinated with their
schedules so that they will be present when
house calls are made.

A notebook should be provided at the
patient’s bedside for everyone involved to
communicate with each other on care proce-
dures, problems that arise in treatment and the
route of the disease.

Education on decubitus has been insufficient
up to now, but recently some good books are
available by Muraki1) and Miyachi8). The most
basic reference is Miyachi’s Guidelines for the
Prevention and Treatment of Decubitus (Bed-
sore),8) which should be used for training
caregivers in the field.

Conclusion

The Japan Organization of Clinical Derma-
tologists has been actively involved in home
medical care for the past two years. The copy
phrase for a poster now being prepared reads,
“Dermatologists make house calls for bed-
sores, eczema, and the like.” As a dermatolo-
gist, I too intend to be actively involved in the
home care and treatment of decubitus.

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Characteristic Diagnostic Imaging Findings in Alzheimer’s Disease

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Abstract: There are characteristic neuroimaging findings in Alzheimer’s disease. X-ray computed tomography (CT) and magnetic resonance imaging (MRI) reveal cerebral atrophy. The atrophy is recognized in the frontal, temporal, and parietal lobes, but not in the occipital lobe. Dilation of the inferior horn, which reflects the atrophy of the medial temporal cortex, is a characteristic finding in Alzheimer’s disease, but, cerebral atrophy is a nonspecific finding. MRI is superior as method of detecting atrophy of the hippocampus. Estimation of hippocampal volume is useful for differentiation between Alzheimer’s disease and a normal brain but it is not practical because the method is complicated. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) reveal reduced blood flow and metabolism in the temporal and the parietal cortex. Reduced blood flow and metabolism in the posterior cingulate cortex are detected by analysis using three-dimensional stereotactic surface projections. These findings are also recognized in the early stage of Alzheimer’s disease. Since functional changes in the brain, namely reduction of cerebral blood flow and metabolism, precede the morphological changes, SPECT and PET are more useful for the early diagnosis of Alzheimer’s disease than CT and MRI.

Key words: Alzheimer’s disease; Cerebral blood flow; SPECT; MRI

Introduction

Almost three years have passed since therapeutic drugs for the treatment of Alzheimer’s disease were approved in Japan. In view of such approval, it has become increasingly more important to make a definitive diagnosis of Alzheimer’s disease. In clinical practice, the diagnosis as Alzheimer’s disease may be made based on the clinical course of dementia, the neurological and neuropsychological findings, and the diagnostic imaging findings on brain...
x-ray computed tomography (X-CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT). Since the various diagnostic imaging procedures provide good evidence for the diagnosis of Alzheimer’s disease, I describe in this paper, the characteristic imaging findings in Alzheimer’s disease.

**X-CT**

X-CT, which is widely employed and easily performed, allows detection of morphological changes. Cerebral atrophy, which is a macroscopic pathological finding in Alzheimer’s disease, can be detected by X-CT, although it is not specific for the diagnosis of Alzheimer’s disease (Fig. 1).

Findings suggestive of cerebral atrophy include ventricular dilatation and widening of sulci; dilatation of the inferior horn, which reflects atrophy of the medial temporal lobe including the hippocampus related to memory impairment, is one of the characteristic findings. In the early stage, cerebral atrophy in Alzheimer’s disease cannot be differentiated from that associated with normal ageing, but more significant atrophy than that seen as a normal ageing variation is increasingly revealed with the passage of time. Even in Alzheimer’s disease patients with severe dementia, only mild or no atrophy of the occipital lobe or cerebellum may be seen. A low-density area surrounding the ventricle, i.e., periventricular low density (PVL), a characteristic finding in cases of vascular dementia, may also be observed in Alzheimer’s disease. The PVL in Alzheimer’s disease, however, is rarely marked. Determination of the presence or absence of lesions associated with cerebrovascular accident (CVA), such as hemorrhage and infarction, is also im-

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**Fig. 1  Time-course changes in X-CT findings in Alzheimer’s disease**

The image taken in 1991 reveals mild cerebral atrophy with dilatation of the inferior horn. With the passage of time, the extent of atrophy increased, and a PVL also became increasingly apparent.
important for the differentiation of Alzheimer’s disease from vascular dementia.

While lesions associated with CVA may also be observed occasionally in some patients who are clinically considered to have Alzheimer’s disease, Alzheimer’s disease can be differentiated from vascular dementia on the basis of the pattern of occurrence of the symptoms of dementia, the course of the dementia, and of whether the site of lesion is related to higher brain functions. In Pick’s disease and fronto-temporal lobar degeneration (FTLD), dilatation of the anterior horn of the lateral ventricle is marked even in the early stages, and atrophy of these lobes is observed. These findings are useful for differentiating these diseases from Alzheimer’s disease. Alzheimer’s disease can, however, hardly be differentiated by X-CT from dementia with Lewy bodies, or Parkinson’s disease with dementia (parkinsonism-dementia complex).

As to the usefulness of X-CT in making an early diagnosis of Alzheimer’s disease, there are no characteristic findings on X-CT in the early stages of Alzheimer’s disease, and only nonspecific findings, such as cerebral atrophy mentioned above, which cannot be easily differentiated from that associated with normal ageing, are observed. Thus, X-CT cannot be considered useful for making an early diagnosis of Alzheimer’s disease.

**MRI**

Cerebral atrophy, similar to that observed by X-CT, is also observed in MR images. Since MRI can provide images of slices parallel to the long axis of the hippocampus and of coronal sections, atrophy of the medial temporal lobe including the hippocampus related to memory,
can be evaluated (Fig. 2). In its usefulness in this regard, MRI differs from X-CT. When the diagnosis of Alzheimer’s disease on MR images was attempted by visually evaluating the atrophy of the hippocampus and amygdala on T1-enhanced images of coronal sections, it was found that observation of atrophy of the anterior portion of the hippocampus was the most useful feature, with a sensitivity of 83%, and specificity of 80% in healthy individuals and 87% in depressed patients.

While atrophy of the hippocampus can be seen more distinctly in patients with advanced dementia than in normal persons, it may be visually obscure in patients with early-stage dementia. However, some reports have shown that the differences in the extent of atrophy between patients with Alzheimer’s disease and normal persons can be appreciated by determination of the area and volume of the hippocampal region. A volumetric evaluation indicated that the volume of the hippocampus was 39.4% lesser in Alzheimer’s disease patients than in controls, and that the sensitivity and specificity of this measurement, which were 95% and 92%, respectively, are useful for making the diagnosis of Alzheimer’s disease; Alzheimer’s disease is diagnosed when the volume of the hippocampus is less than 2.2 cm³. However, in the clinical setting, volumetric evaluation is not very practical, since the procedure for determination of the volume and area of the hippocampus is not a simple or easy one.

Besides PVL, a high-intensity area sur-
rounding the ventricle, i.e., periventricular high intensity (PVH), is also frequently observed in cases of vascular dementia; PVH may be observed in patients with Alzheimer’s disease as well. It is usually mild to moderate, and is frequently observed in cases with advanced dementia.

SPECT

While mainly the morphological changes are detected by X-CT and MRI, PET and SPECT images reflect the cerebral blood flow and metabolism. Thus, functional changes in the brain can be determined by PET and SPECT, because both cerebral blood flow and metabolic rate are correlated with the function of nerve cells. For this reason, PET and SPECT images have come to be called functional images of the brain.

SPECT allows imaging of the cerebral blood flow and measurement of the cerebral blood flow. Areas of reduced blood flow, depending on the pathological stage of the disease are detected by SPECT, while only nonspecific findings of atrophy are observed by X-CT and MRI. Typically, reduced cerebral blood flow is observed in the temporal and parietal lobes in the early stage of the disease, and in the terminal stage, reduced cerebral blood flow in the frontal lobe is observed in addition. Blood flow in the cerebellum and primary sensori-motor area is relatively well maintained until the very late stage. (Fig. 3).

Reduction of cerebral blood flow in an area extending from the temporal lobe to the parietal lobe is a characteristic finding that supports the diagnosis of Alzheimer’s disease. In vascular dementia, reduced blood flow may be observed by SPECT in areas distant from the

![Fig. 4 Z-score images 123I-IMP SPECT analyzed by 3D-SSP in Alzheimer’s disease.](image)
lesion, in addition to local areas of reduced blood flow consistent with hemorrhagic lesions and infarcts as revealed by X-CT and MRI. SPECT may reveal relatively more severe reduction in blood flow in the frontal lobe in cases of vascular dementia. In Pick's disease and dementia due to degeneration of the frontal and temporal lobes, reduced blood flow in the anterior parts of the brain, i.e. the frontal and temporal lobes, is commonly observed, while in Alzheimer's disease, reduced blood flow is observed in more posterior parts of the brain. Diseases associated with dementia thus show characteristic patterns of reduced blood flow; e.g., progressive supranuclear palsy is characterized by reduced blood flow in the cingulate gyrus and Huntington’s disease is characterized by reduced blood flow in the caudate nucleus. These findings are useful for differential diagnosis.

The methods for the diagnosis of Alzheimer's disease from SPECT images include the visual evaluation method, and evaluation of the values obtained in set regions of interest (ROI) on the image. The statistical analysis methods include statistical parametric mapping (SPM) and three-dimensional stereotactic surface projections (3D-SSP).

Each method has its own merits and demerits. The visual evaluation method needs experience. In the method where cerebral blood flow is calculated in ROI, it is difficult to compare all the areas. In 3D-SSP, functional images of the brain are evolved into a standard stereotactic brain coordinate system, and cerebral cortical blood flow is extracted three-dimensionally for reconstruction. The data are statistically compared with the database composed of many images taken in normal subjects processed in a way similar to that of the relevant data, and the sites of reduced blood flow are three-dimensionally displayed as a statistical image. Since the areas of reduced cerebral blood flow are displayed on the images, it becomes easy to make a diagnosis even if the physician is inexperienced.

3D-SSP analysis allows visual evaluation of areas of reduced blood flow; Alzheimer’s disease shows reduced blood flow in the posterior cingulate gyrus, in addition to reduced blood flow in the parietal lobe and lateral temporal lobe (Fig. 4). Reduced blood flow in the posterior cingulate gyrus, which can scarcely be determined on usual axial images, is a characteristic finding of Alzheimer’s disease. SPM analysis results are also similar to the findings of 3D-SSP.

**PET**

PET images reflect the cerebral oxygen consumption rate and cerebral glucose metabolic rate, in addition to the cerebral blood flow. Similar to the findings in SPECT images, areas of reduced cerebral blood flow and metabolism can be observed, depending on the pathological stage of the disease. Since blood flow is correlated with metabolism, a similar pattern of reduction of metabolism is noted in PET images to that in SPECT images.

It has been indicated that \(^{18}\)F-fluorodeoxy-glucose-PET \((^{18}\) FDG-PET\) is useful for differentiation of Alzheimer’s disease from diffuse Lewy-body disease, the incidence of which has been believed to be only second to that of Alzheimer’s disease. When the findings in Alzheimer’s disease and diffuse Lewy-body disease were compared, it was found that the decrease in the cerebral glucose metabolic rate was more marked in diffuse Lewy-body disease, and was more clearly observed in the lateral and medial occipital lobe. Alzheimer’s disease was differentiated from diffuse Lewy-body disease based on the minimum relative values of cerebral glucose metabolic rate in the occipital cortex in the healthy group, relative to the values in the primary sensori-motor area as reference. This PET method of diagnosis showed a sensitivity of 92% and specificity of 92%, for the differential diagnosis of the two diseases.\(^4\)
Early Diagnosis of Alzheimer's Disease

Functional images of the brain obtained by PET and SPECT, rather than images obtained by X-CT and MRI, may be more useful to detect earlier functional changes in the brain. The following are the characteristic findings of early-stage Alzheimer’s disease:

1) Decrease in the cerebral oxygen metabolic rate in the medial and lateral temporal lobe and parietal lobe in $^{15}$O PET studies.5)

2) Early decrease of cerebral glucose metabolism in the posterior cingulate gyrus as revealed by 3D-SSP.6)

3) In patients at high risk of developing Alzheimer’s disease based on the family history and the presence of ApoE ε4, the cerebral glucose metabolism is decreased in the temporal and parietal lobes and in the posterior cingulate gyrus.7,8)

SPECT images before the occurrence of Alzheimer’s disease and in cases with mild dementia were investigated, and the following were found to be useful findings for making an early diagnosis:

1) Assessment of the time-course of changes in the findings in patients with amnesia due to aging revealed that the reduction in blood flow in the medial temporal lobe became progressively more marked in patients who started to show disturbances in daily living because of memory impairment.9)

2) Assessment of the course in mild Alzheimer’s disease revealed that selectively reduced blood flow is observed in the posterior cingulate gyrus, and with time, reduction of blood flow was also noted in the left hippocampus, left parahippocampal gyrus, left amygdala, and the basal forebrain.10)

3) In patients who were suspected to have Alzheimer’s disease and who could almost definitively be diagnosed to have the disease after 2 years’ observation, the cerebral blood flow was demonstrated to be decreased in the hippocampus, amygdaloid nucleus, posterior cingulate gyrus, anterior part of thalamus, and anterior cingulate gyrus, as compared to that in the controls, suggesting that the occurrence of Alzheimer’s disease can be predicted from SPECT findings.11)

Although there may be some differences in findings due to differences in the test procedures and analysis methods, decrease in cerebral blood flow and reduced metabolism in the medial temporal lobe including the hippocampus and the posterior cingulate gyrus, detected by PET and SPECT, is considered to be an early diagnostic indicator of Alzheimer’s disease.

Conclusions

As described above, differential diagnosis and early diagnosis of Alzheimer’s disease can be made based on characteristic morphological and functional imaging findings. Functional images may be extremely useful for the early diagnosis of Alzheimer’s disease.

REFERENCES


