J Gastroenterol
DOI 10.1007/s00535-014-1021-4

The Japanese Society of Gastroenterology

SPECIAL ARTICLE

Evidence-based clinical practice guidelines for management of colorectal polyps

Shinji Tanaka · Yusuke Saitoh · Takahisa Matsuda · Masahiro Igarashi · Takayuki Matsumoto · Yasushi Iwao · Yasumoto Suzuki · Hiroshi Nishida · Toshiaki Watanabe · Tamotsu Sugai · Ken-ichi Sugihara · Osamu Tsuruta · Ichiro Hirata · Nobuo Hiwatashi · Hiroshi Saito · Mamoru Watanabe · Kentaro Sugano · Tooru Shimosegawa

Received: 25 September 2014 / Accepted: 7 November 2014

Abstract
Background Recently in Japan, the morbidity of colorectal polyp has been increasing. As a result, a large number of cases of colorectal polyps that are diagnosed and treated using colonoscopy has now increased, and clinical guidelines are needed for endoscopic management and surveillance after treatment.
Methods Three committees [the professional committee for making clinical questions (CQs) and statements by Japanese specialists, the expert panelist committee for rating statements by the modified Delphi method, and the evaluating committee by moderators] were organized. Ten specialists for colorectal polyp management extracted the specific clinical statements from articles published between 1983 and September 2011 obtained from PubMed and a secondary database, and developed the CQs and statements. Basically, statements were made according to the GRADE system. The expert panel individually rated the clinical statements using a modified Delphi approach, in which a clinical statement receiving a median score greater than seven on a nine-point scale from the panel was regarded as valid.
Results The professional committee created 91CQs and statements for the current concept and diagnosis/treatment of various colorectal polyps including epidemiology, screening, pathophysiology, definition and classification, diagnosis, treatment/management, practical treatment, complications and surveillance after treatment, and other colorectal lesions (submucosal tumors, nonneoplastic polyps, polyposis, hereditary tumors, ulcerative colitis-associated tumor/carcinoma).
Conclusions After evaluation by the moderators, evidence-based clinical guidelines for management of colorectal polyps have been proposed for 2014.

Keywords Colorectal polyp · Colorectal tumor · Polyposis · GRADE system

Introduction

In Japan, following the westernization of eating habits and with aging of the population, the morbidity of colorectal carcinoma and associated mortality are both increasing. Indeed, it has been said that the 21st century is the era of the large intestine. As the number of cases of colorectal polyps that are diagnosed and treated via colonoscopy has now increased, clinical guidelines are needed for endoscopic management and surveillance after treatment. In April 2012, the National Health Insurance system began offering coverage for expenses incurred for colorectal endoscopic submucosal dissection (ESD). Accordingly, appropriate selection between ESD and endoscopic

The original version of this article appeared in Japanese as "Daicho Polyp Sinryo Guidelines 2014" from the Japanese Society of Gastroenterology (JSGE), published by Nankodo, Tokyo, 2014. Please see the article on the standards, methods, and process of developing the Guidelines (doi: 10.1007/s00535-014-1016-1). The members of the Working Committee are listed in the Appendix in the text.

S. Tanaka (✉) · Y. Saitoh · T. Matsuda · M. Igarashi · T. Matsumoto · Y. Iwao · Y. Suzuki · H. Nishida · T. Watanabe · T. Sugai · K. Sugihara · O. Tsuruta · I. Hirata · N. Hiwatashi · H. Saito · M. Watanabe · K. Sugano · T. Shimosegawa
Guidelines Committee for creating and evaluating the "Evidence-based clinical practice guidelines for management of colorectal polyps", the Japanese Society of Gastroenterology (JSGE), K-18 Building 8F, 8-9-13 Ginza, Chuo, Tokyo 104-0061, Japan
e-mail: colon@hiroshima-u.ac.jp

Published online: 07 January 2015

mucosal resection (EMR) has become more important. In this regard, the Japanese Society of Gastroenterology (JSGE) has established "evidence-based clinical guidelines for management of colorectal polyps" (hereafter referred to as "the Guidelines"). Although the title of the Guidelines mentions colorectal polyps, they include all types of localized colorectal lesions, including superficial neoplastic lesions, early carcinoma, and polyposis.

The Guidelines Creation Committee and Evaluation Committee were established prior to drafting the Guidelines. The Japanese Gastroenterological Association, Japanese Society of Gastrointestinal Cancer Screening, the Japan Gastroenterological Endoscopy Society (JGES), the Japan Society of Coloproctology (JSCP), and the Japanese Society for Cancer of the Colon and Rectum (JSCCR), which are cooperative societies, recommended members to be assigned to these two committees.

In the creation of the Guidelines, the Guidelines Creation Committee drafted clinical questions (CQs) that covered: (1) epidemiology; (2) screening; (3) pathophysiology, definition, and classification; (4) diagnosis; (5) treatment and management; (6) practical treatment; (7) complication and surveillance after treatment; and (8) other colorectal lesions (submucosal tumors, nonneoplastic polyps, polyposis, hereditary tumors, ulcerative colitis-associated tumor/cancer). The Evaluation Committee evaluated the drafts of the CQs, and 91 CQs were established. For each CQ, a document retrieval style was created, and systematic document retrieval was performed by searching PubMed and Igaku Chuo Zassi for articles published between January 1983 and September 2011. For insufficient or unobtainable documents, manual searching was also performed. Subsequently, a structured abstract was created, and both a statement and an explanation were written. The Guidelines Creation Committee determined the grades of recommendations and the levels of evidence after deliberation using the Delphi method. As mentioned in a previous publication [1], the Guidelines were created in accordance with the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system. This draft was evaluated and amended by the Evaluation Committee, which was then presented to members of the JSGE. After obtaining public comments, these comments were discussed, and a final version of the Guidelines was created.

The contents on tumor diagnosis and endoscopic treatment described in the Guidelines partially overlap with those of the previously published 2014 JSCCR Guidelines for the Treatment of Colorectal Cancer [2] and the Colorectal ESD/EMR Guidelines (JGES) [3]. In addition, the committees for these three guidelines closely cooperated with each other to ensure their consistency. Concerning the contents of the Guidelines, this paper mainly introduces CQs for the treatment of colorectal polyps.

Clinical questions (CQ) and statements

CQ. What are the indications for endoscopic resection with respect to the size of adenomas?

- Endoscopic resection should be used for lesions ≥6 mm in size (Recommendation 2 [100 %], level of evidence C). However, endoscopic resection should also be used for diminutive lesions ≤5 mm, flat and depressed lesions, as well as for those indistinguishable from carcinoma (Recommendation 2 [100 %], level of evidence D).

Comment: It is strongly recommended that endoscopic resection be used for lesions ≥6 mm in size because the incidence of carcinoma is higher in lesions ≥6 mm than in those ≤5 mm, and because it is often difficult to distinguish between benign adenomas and carcinomas by colonoscopy alone [4, 5].

According to a study in the UK, if the relative risk for carcinoma in lesions ≤5 mm is considered 1, it increases to 7.2, 12.7, and 14.6 in lesions sized 6–10 mm, 11–20 mm, and >20 mm, respectively. Therefore, all colonic lesions ≥6 mm should be either resected or ablated [4]. From the results of meta-analyses, polypectomy [4] and EMR [6]/ESD [7] can be considered the preferred less invasive treatments for colorectal neoplasia [8, 9]. However, for flat and depressed lesions, endoscopic resection is recommended, since the incidence of carcinoma is even higher in lesions that are ≤5 mm in size than in polypoid lesions [6, 10].

CQ. How should diminutive adenomas that are ≤5 mm in size be managed?

- Diminutive polypoid lesions should be followed up (Recommendation 2 [100 %], level of evidence C). However, endoscopic resection should be performed for diminutive flat and depressed lesions that are difficult to distinguish from adenomas or carcinomas (Recommendation 2 [100 %], level of evidence D).

Comment: Hyperplastic diminutive lesions ≤5 mm in size are acceptable for being followed up by colonoscopy. In diminutive polypoid adenomas ≤5 mm, at least in principle, follow-up is acceptable in the absence of colonoscopic findings suggestive of carcinoma. Flat and depressed lesions suspected of being adenoma or carcinoma on colonoscopy are preferably treated by endoscopic resection. Colonoscopic findings suspicious for carcinoma include the following: (1) expansive appearance (protrusion and overextension of the lesion and/or surrounding normal mucosa such as a submucosal tumor); (2) depressed surface; (3) rough appearance (rough surface without shine); (4) normal mucosa of the border of the tumor in

sessile lesions; and (5) type V pit pattern (irregular or disappearance of surface structure). To confirm these findings, chromoendoscopy or magnifying colonoscopy is recommended [11, 12]. Diminutive lesions should be followed up with annual colonoscopy for 3 years [13, 14].

A cohort study on diminutive colorectal lesions reported that there is little change in either the size or shape of lesions after 2–3 years of follow-up [13]. The incidence of carcinoma in diminutive colorectal lesions in Western countries is reported to range from 0.03 to 0.05 %. According to a large-scale cohort study, the overall incidence of polypectomy-related complications is 0.7 % with a perforation rate of 0.1 % (one per 1,000 resections). In addition, to decrease unnecessary risks for healthy individuals and lower overall costs, endoscopic resection should not be performed for all diminutive colorectal lesions $\leq$5 mm [15, 16].

After resection of colorectal neoplasia, yearly follow-up by colonoscopy is recommended until all colorectal polyps including diminutive lesions have been completely excised, and every 3 years thereafter [14, 17].

CQ. How should hyperplastic polyps be managed?

- Follow-up is recommended for hyperplastic polyps $\leq$5 mm detected in the recto-sigmoid region (Recommendation 2 [100 %], level of evidence D). Endoscopic resection should be performed for lesions $\geq$10 mm detected in the right side of the colon, as they are difficult to discriminate from sessile serrated adenoma/polyps (SSA/P) (Recommendation 2 [100 %], level of evidence D).

Comment: Typical hyperplastic polyps presenting as whitish flat lesions $\leq$5 mm in the recto-sigmoid region should be followed up, as there have been no reports on the association of these lesions with adenoma [18, 19]. Colonoscopy every 10 years is recommended in the case of hyperplastic polyps according to the guidelines of the AGA/ASGE. Endoscopic resection should be used for lesions $\geq$10 mm in size in the right side of the colon, as they are difficult to distinguish from SSA/P; the incidence of carcinoma in such lesions has been reported to be 9.4 % [20].

According to the results of 1,800 cases in two large studies on chemoprevention, the risk of hyperplastic polyps is significantly higher (OR 3.67; $p < 0.001$) in patients with hyperplastic polyps detected at initial examination. Moreover, the risk of relapse of adenomatous polyps is also significantly higher (OR 2.08; $p < 0.01$) in patients with adenomatous polyps detected at initial examination. On the other hand, there is no correlation between the risk of adenoma and detection of hyperplastic polyps at initial examination or between adenomatous polyps and the presence of hyperplastic polyps [18, 19]. It has been hypothesized that adenomatous and hyperplastic polys may have different etiology, since the presence of the former has no correlation with the latter, and vice versa [18, 19].

However, one report has suggested that hyperplastic polyps in the recto-sigmoid region may indicate malignant lesions in the proximal colon, since *BRAF* mutations have been detected in hyperplastic polyps, although additional investigations are needed to clarify potential correlations between hyperplastic polyps and SSA/P [18, 19].

CQ. How should serrated lesions of the colorectum be treated?

- Serrated lesions of the colorectum include sessile serrated adenoma/polyp (SSA/P), traditional serrated adenoma (TSA), and hyperplastic polyp (HP). The former two lesions have potential to develop to adenocarcinoma and thus are recommended to treat (Recommendation 2 [100 %], level of evidence D).

Comment: Serrated lesions of the colorectum include SSA/P, TSA, and HP. SSA/P and TSA may undergo malignant transformation to adenocarcinoma and should thus be treated. SSA/P is associated with *BRAF* mutations and the CpG island methylator phenotype (CIMP), and is considered a precursor lesion of colorectal carcinoma with microsatellite instability [21]. Recent studies have reported that the rate of progression to carcinoma in SSA/P ranges from 1.5 to 20 % [22]. Aggressive resection should be performed for SSA/P [23].

TSA is a protruding lesion with distinct redness that is commonly found in the left side of the colon and rectum. Histologically, TSA is considered to potentially progress to carcinoma, similar to SSA/P. Treatment is therefore indicated for TSA, and resection is indicated for TSA $\geq$5 mm in diameter, similar to common adenomas. As for SSA/P, most studies recommend that lesions $\geq$10 mm in diameter should be resected [24–26]. HP may be a precursor lesion of SSA/P and/or TSA. Treatment is not indicated for HP $\leq$5 mm in diameter.

CQ. What therapy is indicated for laterally spreading tumors (LST)?

- The therapeutic choice between piecemeal EMR and ESD for a large LST should be based on the LST subtype, and use of magnifying endoscopy and endoscopic ultrasonography as appropriate (Recommendation 2 [100 %], level of evidence C).

Comment: LSTs are classified into two types according to morphology: granular type (LST-G) and non-granular type (LST-NG) [27]. Each type has two subtypes. The former consists of a "homogenous type" and a "nodular mixed type", while the latter consists of a "flat elevated type" and

a "pseudo-depressed type". Most LST-Gs are considered adenomatous lesions. Among homogenous-type LST-Gs, the incidence of carcinoma or submucosal invasion is extremely low [28, 29]. Large nodule in a nodular mixed-type LST-G, where submucosal invasion tends to be present [30], should be resected en bloc [31]. An adenomatous LST-G homogenous type can be resected by piecemeal EMR [32]. A flat elevated-type LST-NG should be treated according to preoperative diagnosis. For pseudo-depressed-type LST-NGs, en bloc resection should be performed, since these tumors have a high probability of multifocal submucosal invasion independent of their size or pit pattern [30, 31]. In summary, the indications for ESD or piecemeal EMR are based on the LST subtype; magnifying endoscopy and endoscopic ultrasonography are used as needed.

CQ. What are the indications for endoscopic resection of early colorectal carcinoma?

- An early colorectal carcinoma (Tis/T1) should be treated endoscopically when the possibility of lymph node metastasis is extremely low and en bloc resection is possible (Recommendation none, level of evidence level C).

Comment: There are no reports of lymph node metastasis in intramucosal (Tis) carcinomas, while lymph node metastasis occurs in approximately 10 % of submucosal invasive (T1) carcinomas [33, 34]. Therefore, endoscopic resection is recommended in a Tis or Tl carcinoma that has a low probability of lymph node metastasis. Endoscopic resection is both a therapeutic and important diagnostic method that can be used for total excisional biopsy. Complete resection with a negative vertical margin is indispensable for cure after endoscopic resection of a T1 carcinoma. Endoscopic resection of T1 carcinomas is associated with a risk of positive vertical margins. It is thus necessary to completely resect the carcinoma and ensure that horizontal and vertical margins are negative, enabling both precise pathological diagnosis and curative potential [2].

CQ. What pathological findings do indicate additional surgery after endoscopic resection for early colorectal carcinoma?

- T1 carcinoma with a tumor-positive vertical margin is an absolute indication. T1 carcinoma with an unfavorable histologic grade or submucosal invasion of $\geq$1,000 μm, or vascular invasion or grade 2/3 tumor budding should be considered for additional surgery with lymph node dissection (Recommendation none, level of evidence C).

Comment: Lymph node metastasis is found in 6.8–17.8 % of T1 carcinomas [2, 35, 36]. In principle, T1 carcinoma should be treated by surgery with lymph node dissection. The risk factors for lymph node metastasis in T1 carcinoma include depth of submucosal invasion [2, 35, 37–42], histological grade [2, 35, 37, 39–42], budding grade [2, 35, 36, 43], and vascular invasion [2, 35–44]. According to the 2014 guidelines by the JSCCR (Japanese Society for Cancer of the Colon and Rectum) for the treatment of colorectal carcinoma, among the carcinomas treated by endoscopic resection, T1 carcinomas with a tumor-negative vertical margin, favorable histologic grade with a submucosal invasion depth of <1,000 μm, and absence of vascular invasion with tumor budding grade 1 (low grade) could be followed up, while T1 carcinomas that do not meet these criteria should be considered for additional surgery with lymph node dissection. It may possible to reduce the number of patients undergoing unnecessary additional surgical resection considering the above risk factors [2, 37–39, 45, 46]. Even if the risk for lymph node metastasis after endoscopic treatment cannot be considered zero, a comprehensive assessment of the pathologic findings after endoscopic resection, patient age, physical activity levels, comorbidities, and any potentially undesirable consequences of the resection such as urinary and excretory disorders or the need for colostomy is needed.

CQ. In which types of colorectal tumors is it acceptable to perform piecemeal EMR?

- Definite adenoma or Tis carcinoma based on preoperative diagnosis are acceptable for piecemeal EMR. However, rates of local recurrence with piecemeal resection are high, and thus caution is advised (Recommendation 2 [100 %], level of evidence C).

Comment: In principle, en bloc resection should be used for suspicious or definite carcinoma, since the specimen obtained by complete en bloc resection should be pathologically examined in detail. On the basis of precise preoperative diagnosis with magnifying endoscopy, adenomatous lesions or focal carcinoma in adenomas $\geq$2 cm in diameter, for which en bloc snare EMR is not indicated, can be completely resected using deliberate piecemeal EMR to avoid segmentation of the carcinomatous area without compromising pathological diagnosis [2]. Although the local recurrence rate associated with piecemeal resection is high compared with that after en bloc resection [31, 32, 47–52], most local recurrent lesions are adenomas. Cure is possible with additional endoscopic treatment for local recurrent intramucosal lesions [47, 49, 52, 53]. In contrast, ESD allows complete en bloc resection regardless of lesion size. However, colorectal ESD is

technically more difficult and requires considerable experience.

CQ. What are the indications for endoscopic submucosal dissection?

- (1) Tumors requiring endoscopic en bloc resection, for which the snare technique is difficult to use; (2) intramucosal tumors accompanied by submucosal fibrosis, induced by biopsy or peristalsis of the lesion; (3) sporadic localized tumors that occur as a result of chronic inflammation; and (4) local residual early carcinoma after endoscopic resection are among the indications for ESD (Recommendation none, level of evidence C).

Comment: The Colorectal ESD Standardization Implementation Working Group proposed a draft entitled Criteria of Indications for Colorectal ESD [31]. It specifically states that colorectal ESD is indicated for tumors requiring endoscopic en bloc resection when it is difficult to use the snare technique, such as LST-NG (especially the pseudo-depressed type), tumors with a type VI pit pattern, shallow submucosal invasive carcinoma, large depressed tumors, and large elevated lesions that are probably malignant (large nodular lesions such as LST-G). Other lesions such as intramucosal tumors accompanied by submucosal fibrosis induced by biopsy or peristalsis of the lesion, sporadic localized tumors that occur as a result of chronic inflammation such as ulcerative colitis, and local residual early carcinoma after endoscopic resection, are also included in the indications for ESD. A cure rate of 83–88 % has been reported using ESD for local residual early carcinoma after endoscopic resection [54, 55]. In Japan, colorectal ESD has been covered by national health insurance since April 2012. It is indicated in early colorectal carcinomas, early carcinomas that are 2–5 cm in diameter. However, there were no significant differences in the outcome of colorectal ESD between lesions 2–5 cm in diameter and those $\leq$5 cm in diameter based on a prospective cohort study by the Japan Gastroenterological Endoscopy Society (JGES). Considering payments by national health insurance, no limitations on lesion size have been required for colorectal ESD.

CQ. Is biopsy essential for choosing the therapeutic strategy for colorectal lesions?

- This will depend on the characteristics of individual lesions. It is acceptable to decide a therapeutic strategy for colorectal lesions without biopsy (Recommendation 2 [100 %], level of evidence C).

Comment: Endoscopic procedures, especially magnifying endoscopy such as pit pattern diagnosis or image-enhanced endoscopy, avoid unnecessary biopsy for colorectal tumors. Biopsy should not be performed in polypectomy or EMR, as it increases medical expenses. In addition, it is clinically insignificant to randomly obtain biopsies for protruding lesions, as most are adenoma or carcinoma in adenoma. However, biopsy for a lesion suspected to be T1 carcinoma may acceptable, since histological information is helpful for planning the therapeutic strategy. Biopsy for superficial lesions (flat or depressed lesions) should not be performed prior to endoscopic resection, as it causes false-positive non-lifting signs due to submucosal fibrosis after injection during EMR [56]. It is important to understand whether the lesion is indicated for endoscopic resection through standard or magnifying endoscopic observation.

CQ. How is the choice made from among polypectomy, EMR, and ESD for colorectal tumors?

- Polypectomy is indicated for pedunculated or semi-pedunculated polyps, and EMR is indicated for sessile polyps or superficial lesions. ESD is indicated for lesions requiring endoscopic en bloc resection, although the lesions cannot be resected en bloc by snare techniques (Recommendation 2 [100 %], level of evidence C).

Comment: The choice of technique for endoscopic resection should be based on tumor morphology and size. Polypectomy is normally indicated for pedunculated or adenomatous semi-pedunculated polyps, while EMR is suitable for sessile, semi-pedunculated, or superficial tumors that are likely to be carcinoma [6, 57]. ESD allows complete en bloc resection regardless of the size of the lesion [28, 31, 58, 59]. Colorectal ESD is thus indicated for lesions requiring endoscopic en bloc resection when it is difficult to use the snare technique [31]. Moreover, en bloc resection is particularly indicated for depressed tumors or pseudo-depressed-type LST-NGs, as these tumors have a high incidence of submucosal invasion [28, 29]. In contrast, piecemeal EMR is acceptable for LST-G homogenous-type, since it is associated with a very low incidence of submucosal invasion [31]. EMR or ESD should be preferred over polypectomy for suspected submucosal invasive (T1) carcinoma.

CQ. Does colorectal carcinoma incidence decrease by endoscopic removal of colorectal adenoma?

- It is generally believed that the incidence of colorectal carcinoma decreases following endoscopic removal of colorectal adenomas, at least in Western countries, although there is limited data in Japan (Recommendation none, level of evidence B).

Comment: In 1993, the National Polyp Study (NPS) Workgroup reported that endoscopic removal of all

colorectal adenomatous polyps is associated with a decrease in the incidence of colorectal carcinoma from 76 to 90 % [60]. Since then, endoscopic removal of all adenomas during colonoscopy was strongly recommended in Western countries. In contrast, some Japanese endoscopists have reported that endoscopic polypectomy of all adenomas (especially for diminutive polyps) may not be effective in decreasing the incidence of colorectal carcinoma. Moreover, there is limited data in Japan. Regarding this CQ, two issues should be considered, namely the prevalence of carcinoma based on the size of the lesions and the interval of surveillance after endoscopic polypectomy. Regarding the former, in 1995, Sawada and Hiwatashi reported that the prevalence of carcinoma in patients with diminutive (<5 mm) polyps was 1.2 % (98.8 % were benign adenoma) [61]. While this proportion appears to be higher than that reported in Western countries (0.03–0.05 %), this discrepancy may be related to differences in pathological definitions. Nonetheless, the prevalence of carcinoma in patients with diminutive polyps is rather low. On the other hand, a single screening/surveillance colonoscopy session may not identify all polyps. Moreover, there are many reports concerning the clinical importance of de novo carcinoma. We note that a single colonoscopy with polyp removal is not a flawless procedure, and in particular, poor bowel preparation may be associated with a lower reported incidence of colorectal carcinoma [62–64]. Based on these points, it can be assumed that carcinoma can be prevented by endoscopic removal of polyps.

CQ. How should surveillance colonoscopy be planned after endoscopic removal of colorectal adenoma?

- Follow-up colonoscopy should be performed within 3 years after polypectomy (Recommendation 2 [100 %], level of evidence B).

Comment: The National Polyp Study (NPS) Workgroup recommended an interval of at least 3 years after colonoscopic removal of newly diagnosed adenomatous polyps and follow-up examination [65]. According to the European guidelines [66] and modified US guidelines [67], the most suitable interval for surveillance colonoscopy is recommended based on the number of adenomas, maximum size of polyps, and histopathological findings (including the presence of high-grade dysplasia) of resected lesions. As general guidance, patients with several (in European guidelines: <4, in US guidelines <9) small adenomas (low-grade dysplasia) <10 mm should undergo surveillance colonoscopy at 3 years following polypectomy. In contrast, patients with only one or two small low-grade adenomas should undergo routine screening (i.e., FOBT) according to the European guidelines, and surveillance colonoscopy after 5–10 years according to the US guidelines. Moreover, according to these guidelines, patients with many adenomas (>10) or high-grade dysplasia (known as intramucosal cancer in Japan) should undergo more intensive surveillance colonoscopy. In Japan, the decision to follow these guidelines is uncertain because management of diminutive adenoma (<5 mm) has not been established. In brief, endoscopists in the West attempt to remove all adenomas, whereas there is no uniform Japanese approach (removal or follow-up) for diminutive adenomas, and controversy remains in Japan [68–72]. The present guidelines, therefore, recommend the following based on data from a retrospective study carried out by the Japan Polyp Study Workgroup [73]: "Follow-up colonoscopy should be performed within 3 years after polypectomy."

Acknowledgments This article was supported by a Grant-in-Aid from the JSGE. The authors thank Dr. Shiro Oka (Hiroshima University Hospital) and Dr. Toshiaki Tanaka (University of Tokyo) for great assistance for data collection, data analysis, and manuscript preparation.

Conflict of interest Any financial relationship with enterprises, businesses, or academic institutions in the subject matter or materials discussed in the manuscript are listed as follows; (1) those from which the authors, the spouse, partner or immediate relatives of the authors, have received individually any income, honoraria or any other types of remuneration; Ikagaku Co., Ltd., Abbvie Inc., Eisai Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited., Mitsubishi Tanabe Pharma Corporation; and (2) those from which the academic institutions of the authors received support (commercial/academic cooperation); Asahi Kasei Medical Co., Ltd., Ajinomoto Pharmaceuticals Co., Ltd., Astellas Pharma Inc., AstraZeneca K.K., Abbvie Inc., Eisai Co., Ltd., MSD K.K., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Jimro Co., Ltd., GeneCare Research Institute Co., Ltd., Suzuken Co., Ltd., Zeria Pharmaceutical Co., Ltd., Century Medical, Inc., Daiichi Sankyo Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Company Limited., Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical Co., Ltd., Toray Industries, Inc., Bristol-Myers Squibb Company, Yakult Honsha Co., Ltd., UCB Japan Co. Ltd.

Appendix

Members of the Working Committee who created and evaluated the "Evidence-based clinical guidelines for management of colorectal polyps", JSGE

Director Responsible

Mamoru Watanabe (Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University)

Executive Committee

Chair: Shinji Tanaka (Department of Endoscopy, Hiroshima University Hospital)

Vice-Chair: Yusuke Saitoh (Digestive Disease Center, Asahikawa City Hospital)

Members: Takayuki Matsumoto (Division of Gastroenterology, Iwate Medical University), Takahisa Matsuda (Endoscopy Division, National Cancer Center Hospital), Yasushi Iwao (Center for Preventive Medicine, Keio University Hospital), Masahiro Igarashi (Department of Endoscopy, Cancer Institute Ariake Hospital), Yasumoto Suzuki (Coloproctology Center, Matsushima Clinic), Hiroshi Nishida (Occupational Health Center, Panasonic Health Insurance Organization), Toshiaki Watanabe (Department of Surgical Oncology, University of Tokyo), Tamotsu Sugai (Department of Molecular Diagnostic Pathology, Iwate Medical University).

Evaluation Committee

Chair: Ken-ichi Sugihara (Department of Surgical Oncology, Tokyo Medical and Dental University)

Vice-Chair: Osamu Tsuruta (Digestive Disease Center and GI Endoscopy, Kurume University Hospital)

Members: Ichiro Hirata (Department of Gastroenterology, Fujita Health University School of Medicine), Nobuo Hiwatashi (Department of Gastroenterology, Iwaki Kyoritsu General Hospital), Hiroshi Saito (Research Center for Cancer Prevention and Screening, National Cancer Center).

The Japanese Society of Gastroenterology

President: Tooru Shimosegawa (Division of Gastroenterology, Tohoku University Graduate School of Medicine)

Former President: Kentaro Sugano (Jichi Medical University)

References

1. Yoshida M, Kinoshita Y, Watanabe M, JSGE clinical practice guidelines, et al. Standards, methods, and process of developing the guidelines. J Gastroenterol. 2014;. doi:10.1007/s00535-014-1016-1.
2. JSCCR Guidelines 2014 for the Treatment of Colorectal Cancer, published by Kanahara, Tokyo, 2014 (in Japanese, English version under preparation).
3. Tanaka S, Kashida H, Saito Y, et al. JGES Colorectal ESD/EMR Guidelines. Gastroenterol Endosc. 2014;56:1598–617 (in Japanese, English version under preparation).
4. Aldridge AJ, Simson JN. Histological assessment of colorectal adenomas by size. Are polyps less than 10 mm in size clinically important? Eur J Surg. 2001;167:777–81.
5. Ahlawat SK, Gupta N, Benjamin SB, et al. Large colorectal polyps: endoscopic management and rate of malignancy: does size matter? J Clin Gastroenterol. 2011;45:347–54.
6. Kudo S. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy. 1993;25:455–61.
7. Tanaka S, Oka S, Kaneko I, et al. Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. Gastrointest Endosc. 2007;66:100–7.
8. Puli SR, Kakugawa Y, Gotoda T, et al. Meta-analysis and systematic review of colorectal endoscopic mucosal resection. World J Gastroenterol. 2009;15:4273–7.
9. Puli SR, Kakugawa Y, Saito Y, et al. Successful complete cure en-bloc resection of large non pedunculated colonic polyps by endoscopic submucosal dissection: a meta-analysis and systematic review. Ann Surg Oncol. 2009;16:2147–51.
10. Saitoh Y, Waxman I, West AB, et al. Prevalence and distinctive biological features of flat colorectal adenomas in a North American population. Gastroenterology. 2001;120:1657–65.
11. Saitoh Y, Iwashita A, Kudo S, et al. Result of project research [Management of colorectal diminutive lesions] in Japanese society for cancer for colon and rectum—guiding principle of endoscopic treatment for colorectal diminutive lesions with 5 mm or less. Stomach Intestine. 2009;44:1047–51 (in Japanese).
12. Tanaka S, Kaltenbach T, Chayama K, et al. High-magnification colonoscopy (with videos). Gastrointest Endosc. 2006;64:604–13.
13. Onoue K, Yamada H, Miyazaki T, et al. Natural history of colorectal diminutive polyps with 5 mm or less-prospective study. J Gastrointestinal Cancer Screen. 2008;46:729–34 (in Japanese with English abstract).
14. Toyonaga N, Nishino H, Suzuki Y, et al. Appropriate surveillance method after endoscopic resection of colorectal neoplasia. Gastroenterol Endosc. 2009;51:1121–8 (in Japanese with English abstract).
15. Gschwantler M, Kriwanek S, Langner E, et al. High-grade dysplasia and invasive carcinoma in colorectal adenomas: a multivariate analysis of the impact of adenoma and patient characteristics. Eur J Gastroenterol Hepatol. 2002;14:183–8.
16. Bretagne JF, Manfredi S, Piette C, et al. Yield of high-grade dysplasia based on polyp size detected at colonoscopy: a series of 2,295 examinations following a positive fecal occult blood test in a population-based study. Dis Colon Rectum. 2010;53:339–45.
17. Togashi K, Shimura K, Konishi F, et al. Prospective observation of small adenomas in patients after colorectal cancer surgery through magnification chromo colonoscopy. Dis Colon Rectum. 2008;51:196–201.
18. Bensen SP, Cole BF, Mott LA, et al. Colorectal hyperplastic polyps and risk of recurrence of adenomas and hyperplastic polyps. Polyps prevention study. Lancet. 1999;354:1873–4.
19. Laiyemo AO, Murphy G, Sansbury LB, et al. Hyperplastic polyps and the risk of adenoma recurrence in the polyp prevention trial. Clin Gastroenterol Hepatol. 2009;7:192–7.
20. Hasegawa S, Tsuruta O, Kawano H, et al. Endoscopic diagnosis of colonic serrated lesion—conventional endoscopic findings. Stomach Intestine. 2011;46:394–404 (in Japanese with English abstract).
21. Legget B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterology. 2010;138:2088–100.
22. Yoshimori K, Tsuruta O, Kawano H, et al. Serrated adenoma-endoscopic findings and treatment. Early Colorectal Cancer. 2006;10:291–6 (in Japanese with English abstract).
23. De Jesus-Monge WE, Gonzalez-Keelan MC, Cruz-Correa M. Serrated adenomas. Curr Gastroenterol Rep. 2009;11:420–7.
24. Matumoto T, Mizuno M, Shimizu M, et al. Clinico pathological features of serrated adenoma of the colorectum: comparison with traditional adenoma. J Clin Pathol. 1999;52:513–6.
25. Kashida H, Kudo S. New knowledge of colorectal polyp-concept, characters and diagnosis. J of Clinical and Experimental Medicine (IGAKU NO AYUMI) 2006 Supplement ver3:628–633 (in Japanese).
26. Uraoka T, Higashi R, Ohara N, et al. Endoscopic findings with magnification of serrated lesions in the colorectum. Stomach Intestine. 2011;46:406–16 (in Japanese with English abstract).
27. Kudo S, Lambert R, Allen JI, et al. Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc. 2008; 68(Suppl):S3–47.
28. Saito Y, Fujii T, Kondo H, et al. Endoscopic treatment for laterally spreading tumors in the colon. Endoscopy. 2001;33:682–6.

29. Nishiyama H, Isomoto H, Yamaguchi N, et al. Endoscopic submucosal dissection for laterally spreading tumours of the colorectum in 200 consecutive cases. Surg Endosc. 2010;24:2881–7.
30. Uraoka T, Saito Y, Matsuda T, et al. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. Gut. 2006;55:1592–7.
31. Tanaka S, Oka S, Chayama K. Colorectal endoscopic submucosal dissection: present status and future perspective, including its differentiation from endoscopic mucosal resection. J Gastroenterol. 2008;43:641–51.
32. Tanaka S, Haruma K, Oka S, et al. Clinicopathologic features and endoscopic treatment of superficially spreading colorectal neoplasms larger than 20 mm. Gastrointest Endosc. 2001;54:62–6.
33. Coverlizza S, Risio M, Ferrari A, et al. Colorectal adenomas containing invasive carcinoma: pathologic assessment of lymph node metastatic potential. Cancer. 1989;64:1937–47.
34. Kodahira S, Yao T, Nakamura K, et al. Submucosal invasive carcinoma of the colon and rectum with metastasis—analysis of 1,917 cases focused of sm invasion. Stomach Intestine. 1994;29:1137–42 (in Japanese).
35. Nakadoi K, Tanaka S, Kanao H, et al. Management of T1 colorectal carcinoma with special reference to criteria for curative endoscopic resection. J Gastroenterol Hepatol. 2012;27:1057–62.
36. Suh JH, Han KS, Kim BC, et al. Predictors for lymph node metastasis in T1 colorectal cancer. Endoscopy. 2012;44:590–5.
37. Son HJ, Song SY, Lee WY, et al. Characteristics of early colorectal carcinoma with lymph node metastatic disease. Hepatogastroenterology. 2008;55:1293–7.
38. Kim JH, Cheon JH, Kim TI, et al. Effectiveness of radical surgery after incomplete endoscopic mucosal resection for early colorectal cancers: a clinical study investigating risk factors of residual cancer. Dig Dis Sci. 2008;53:2941–6.
39. Tanaka S, Yokota T, Saito D, et al. Clinicopathologic features of early rectal carcinoma and indications for endoscopic treatment. Dis Colon Rectum. 1995;38:959–63.
40. Tanaka S, Haruma K, Oh-e H, et al. Conditions of curability after endoscopic resection for colorectal carcinoma with submucosally massive invasion. Oncol Rep. 2000;7:783–8.
41. Oka S, Tanaka S, Kanao H, et al. Mid-term prognosis after endoscopic resection for submucosal colorectal carcinoma: summary of a multicenter questionnaire survey conducted by the colorectal endoscopic resection standardization implementation working group in Japanese Society for Cancer of the Colon and Rectum. Dig Endosc. 2011;23:190–4.
42. Okabe S, Arai T, Maruyama S, et al. A clinicopathological investigation on superficial early invasive carcinomas of the colon and rectum. Surg Today. 1998;28:687–95.
43. Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology. 2004;127:385–94.
44. Meining A, von Delius S, Eames TM, et al. Risk factors for unfavorable outcomes after endoscopic removal of submucosal invasive colorectal tumors. Clin Gastroenterol Hepatol. 2011;9:590–4.
45. Yoda Y, Ikematsu H, Matsuda T, et al. Long-term outcomes of submucosal invasive colorectal cancer. Stomach Intestine. 2011;46:1442–8 (in Japanese with English abstract).
46. Ikematsu H, Yoda Y, Matsuda T, et al. Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology. 2013;144:551–9.
47. Tamura S, Nakajo K, Yokoyama Y, et al. Evaluation of endoscopic mucosal resection for laterally spreading rectal tumors. Endoscopy. 2004;36:306–12.
48. Luigiano C, Consolo P, Scaffidi MG, et al. Endoscopic mucosal resection for large and giant sessile and flat colorectal polyps: a single-center experience with long-term follow-up. Endoscopy. 2009;41:829–35.
49. Mannath J, Subramanian V, Singh R, et al. Polyp recurrence after endoscopic mucosal resection of sessile and flat colonic adenomas. Dig Dis Sci. 2011;56:2389–95.
50. Hurlstone DP, Sanders DS, Cross SS, et al. Colonoscopic resection of lateral spreading tumours: a prospective analysis of endoscopic mucosal resection. Gut. 2004;53:1334–9.
51. Saito Y, Fukuzawa M, Matsuda T, et al. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection. Surg Endosc. 2010;24:343–52.
52. Terasaki M, Tanaka S, Oka S, et al. Clinical outcomes of endoscopic submucosal dissection and endoscopic mucosal resection for laterally spreading tumors larger than 20 mm. J Gastroenterol Hepatol. 2012;27:734–40.
53. Tanaka S, Terasaki M, Hayashi N, et al. Warning for unprincipled colorectal endoscopic submucosal dis- section: accurate diagnosis and reasonable treatment strategy. Dig Endosc. 2013;25:107–16.
54. Hurlstone DP, Shorthouse AJ, Brown SR, et al. Salvage endoscopic submucosal dissection for residual or local recurrent intraepithelial neoplasia in the colorectum: a prospective analysis. Colorectal Dis. 2008;10:891–7.
55. Kuroki Y, Hoteya S, Mitani T, et al. Endoscopic submucosal dissection for residual/locally recurrent lesions after endoscopic therapy for colorectal tumors. J Gastroenterol Hepatol. 2010;25:1747–53.
56. Dirschmid K, Kiesler J, Mathis G, et al. Epithelial misplacement after biopsy of colorectal adenomas. Am J Surg Pathol. 1993;17:1262–5.
57. Deyhle P, et al. A method for endoscopic electro resection of sessile colonic polyps. Endoscopy. 1973;5:38–40.
58. Kobayashi N, Saito Y, Uraoka T, et al. Treatment strategy for laterally spreading tumors in Japan: before and after the introduction of endoscopic submucosal dissection. J Gastroenterol Hepatol. 2009;24:1387–92.
59. Nakajima T, Saito Y, Tanaka S, et al. Current status of endoscopic resection strategy for large, early colorectal neoplasia in Japan. Surg Endosc. 2013;27:3262–70.
60. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 1993;329:1977–81.
61. Sawada T, Hiwatashi N, et al. Report from the workgroup of Ministry of Health. Labor Welf. 1995;H6:66–72 (in Japanese).
62. Igarashi M, Katsumata T. How to follow the residual colorectal polyps? (Chapter; How should we perform colorectal polypectomy? Edit: Tada S, Kudo S, Nihon Medical Center, Tokyo, 1997: 155–160 (in Japanese).
63. Nozaki R, Takagi K, Takano M, et al. Clinical investigation of colorectal cancer detected by follow-up colonoscopy after endoscopic polypectomy. Dis Colon Rectum. 1997;40:S16–22.
64. Nusko G, Hahn EG, Mansmann U. Risk of advanced metachronous colorectal adenoma during long-term follow-up. Int J Colorectal Dis. 2008;23:1065–71.
65. Winawer SJ, Zauber AG, O'Brien MJ, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Work group. N Engl J Med. 1993;328:901–6.
66. Atkin WS, Valori R, Kuipers EJ, et al. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition- Colonoscopic surveillance following adenoma removal. Endoscopy. 2012;44(Suppl 3):S151–63.
67. Lieberman DA, Rex DK, Winawer SJ, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a

consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143:844–57.
68. Suzuki Y, Matsuike T, Nozawa H, et al. Treatment strategy for colorectal polyps and surveillance method by total colonoscopy. Ther Res. 1997;18:S362–5 (in Japanese).
69. Fukutomi Y, Moriwaki H, Nagase S, et al. Metachronous colon tumors: risk factors and rationale for the surveillance colonoscopy after initial polypectomy. J Cancer Res Clin Oncol. 2002;128:569–74.
70. Yamaji Y, Mitsushima T, Ikuma H, et al. Incidence and recurrence rates of colorectal adenomas estimated by annually repeated colonoscopies on asymptomatic Japanese. Gut. 2004;53:568–72.
71. Asano M, Matsuda Y, Kawai M, et al. Long-term outcome and surveillance after endoscopic removal for colorectal adenoma: from the viewpoint of the cases with multiple colorectal polyps. Dig Med. 2006;43:299–306 (in Japanese).
72. Kawamura T, Ueda M, Cho E. Surveillance after colonoscopic removal of adenomatous polyps. Dig Med. 2006;43:307–10 (in Japanese).
73. Matsuda T, Fujii T, Sano Y, et al. Five-year incidence of advanced neoplasia after initial colonoscopy in Japan: a multicenter retrospective cohort study. Jpn J Clin Oncol. 2009;39:435–42.

総論

大腸がん検診のあり方——最近のエビデンスを踏まえて

Author 斎藤 博 国立がん研究センターがん予防・検診研究センター検診研究部

KeyWords ◎大腸がん検診 ◎エビデンス ◎便潜血検査 ◎大腸内視鏡検査

Headline

1 便潜血検査による大腸がん検診は，その有効性ががん検診の中でも最も確立している．
2 sigmoidoscopyによる検診の有効性も確立している．
3 健常者では初回の内視鏡検診で異常がなければ，そうでない場合に比べ10年以上の長期にわたって浸潤がんのリスクが低い可能性が示されている．

本稿に与えられたテーマは，消化器がん診療において最近大きな変化が起こっている領域の一つである大腸がん検診について最新知見を提供することである．大腸がん検診に関連するエビデンスとしては，内視鏡，特にsigmoidoscopyによる検診に関する有効性が確立したことが特筆すべき成果であり，colonoscopyの検診についても評価できる質の研究報告が出始めている．またスクリーニング以外にも，検診関連事項としてポリープ切除後のリスクについても以前から若干の知見は積まれている．それらを踏まえると，スクリーニングおよび発見ポリープのマネジメント等について，より具体的かつ合理的な判断が可能である．たとえばこれまで腺腫が見つかった場合には過剰なフォローアップの内視鏡が行われてきたが，一定の間隔を開ける根拠が示されている．

大腸がんの死亡率・罹患率

大腸がんは過去40年以上にわたってその死亡率が増加を続け，わが国の主たるがん死亡の原因となっている．部位別年齢調整死亡率は，女性では2003年から第1位，男性でも2007年から第3位と男女を通じて高く，わが国のがん対策において重要度の高いがんである[1]．1990年以降はその増加が止まり現在ではやや減少に転じているが，今後もわが国の主要ながんであり続けると考えられる．

大腸がん検診およびスクリーニング法の位置づけ

検診を行う第一の条件は，健康対策上の重要な課題であること(表1)，つまりがん検診の場合は死亡率や罹患率が高いことであり，その意味で大腸がんは世界の先進国に共通の検診の対象がんである．また大腸がん検診は便潜血検査(faecal occult blood test:FOBT)による死亡率減少，さらに罹患率の減少効果も実証されており[2,3]がん検診の中でもそれを対策として行う条件に最も合致しているといえ，世界的にその導入が進んでいる．

大腸がん検診については，次項に要約するように内視鏡による検診についても最近エビデンスが確立しつつある．しかし内視鏡検診はそのキャパシティー，偶発症などの不利益が懸念される他，施策としてのがん検診の条件[4]を満足するには至っておらず，内視鏡は施策としての検診においては精検の位置づけである．スクリーニング法は便潜血検査であり，その精密検査として大腸内視鏡検査を行うのが世界のプロ

0370-999X/15/¥100/頁/JCOPY

グラムの概要である.

スクリーニングのエビデンス(科学的根拠)

1. 便潜血検査(FOBT)(表2)

a) 化学法FOBT(化学法)の死亡率減少効果

大腸がん検診は欧米で1960年代に開発されたグアヤックろ紙法による化学法FOBTについて,複数のランダム化比較試験(randomized controlled trial:RCT)が行われ,一致して検診による死亡率減少効果が示されている.他のがん検診でRCTによる有効性のエビデンスがあるものはマンモグラフィによる乳がん検診があげられるが,RCTの結果は一致していない.有効性の証拠の水準が最上位であるRCTがすべて一致して有効性を示しているFOBTによる大腸がん検診は,がん検診の中で最も明確に科学的根拠が確立していることをまず認識したい(表2)[3].

最初の米国ミネソタ研究では逐年群で33%の死亡率低下[2],隔年群でも21%の低下が観察された.さらに,逐年,隔年の間隔での検診について罹患率の減少も示され,スクリーニングにより浸潤がんが減少する(逐年で20%,隔年で17%)ことも明らかとなった[5].最近,同研究の30年の長期観察後の効果が逐年,2年間隔でそれぞれ大腸がん死亡率は32%,22%低下したと報告され,有効性が長期にわたって確認された.

ミネソタ研究以外に欧州で行なわれた英国とデンマークの2研究,さらにフランスにおける地域ブロック割付による1研究で隔年検診により,15~18%の死亡率低下が観察され,複数のメタ解析ではいずれも14~16%の死亡率低下を示した[3].

b) 免疫法FOBT(免疫法)に関する死亡率減少効果

わが国で始まった免疫法FOBTは,有効性の科学的根拠としてはRCTはなく,日本からの4件を含めた5件の症例対照研究と1件のコホー

表1 スクリーニングの基準—Wilson & Junger screening criteria

1. その疾患が健康上の重大な問題になっている
2. 患者に対して認められた治療がある
3. 診断と治療を行う機関がある
4. 診断可能な無症状または症状のある早期の段階がある
5. 適切な検査がある
6. 検査法は集団に受け容れられるものである
7. 潜伏期からの進展など疾患の自然史が十分把握されている
8. 誰を患者として治療すべきか合意の得られた方針がある
9. (診断・治療を含め)スクリーニング*のコストが医療費全体とバランスがとれる
10. スクリーニング*は継続的なプロセスで一回こっきりではない

*:Case finding
(WHO 1968)

表2 便潜血検査の有効性に関する主な証拠—化学法

年	報告者	Journal	地域	研究デザイン	スクリーニング法 検診間隔, 対象年齢	RR(95% CI) 罹患	RR(95% CI) 死亡
1993, 1999 2000	Mandel	N Engl J Med	US Minnesota	RCT	逐年・隔年 50~80	逐年 0.80(0.70-0.90) 隔年 0.83(0.73-0.94)	逐年 0.67(0.50-0.87) 隔年 0.80(0.70-0.90)
1996, 2002	Hardcastle	Lancet	UK Nottingham	RCT	隔年 45~74	/	0.85(0.74-0.98)
1996, 2002	Kronborg	Lancet	Denmark Funen	RCT	隔年 45~75	/	0.82(0.68-0.99)
2004	Faivre	Gastroenterology	French	RCT	隔年 45~74	1.01(0.91-1.12)	0.84(0.71-0.99)

RCT:randomized controlled trial

表3　便潜血検査の有効性に関する主な証拠―免疫法

年	FOBT	報告者	Journal	地域	研究デザイン	検診間隔・対象年齢	RR(95% CI) 罹患	死亡
1993	免疫法	Hiwatashi	Jpn J Cancer Res	Japan	CCS	逐年 45～69	/	0.24(0.08-0.76)
1995	免疫法単独	Saito	Int J Cancer	Japan	CCS	逐年 40～79	/	0.40(0.17-0.92)
1997	免疫法＋化学法	Zappa	Int J Cancer	Italy Florence	CCS	隔年 41～75	/	0.54(0.3-0.9)
2000	免疫法＋化学法	Saito	Oncol Rep	Japan	CCS	逐年 >40	/	逐年 0.20(0.08-0.49) 隔年 0.17(0.04-0.75)
2003	免疫法単独	Nakajima	Br J Cancer	Japan	CCS	逐年・隔年 40～79	進行がん 0.54(0.29-0.99)	/
2007	免疫法（＋化学法）	Lee	Cancer Causes Control	Japan	Cohort	40～59	進行がん 0.41(0.27-0.63)	0.28(0.13-0.61)

ト研究が報告されている(表3)[3]．死亡率減少効果に関する免疫法単独による研究は1研究のみであるが，FOBT 1日法の逐年検診により60%の死亡率が減少すると示唆されている[16]．ほかの一部化学法を含む検診に関する4研究もあわせ，一致して死亡リスク減少効果を示す結果が示され，リスク低下は46～80%と報告されている．また進行がんのリスク低下も報告されている[3](表3)．

c）FOBTの感度

化学法については研究対象の全例に内視鏡とFOBTを行い，内視鏡を基準としてFOBTで1回スクリーニングする感度(スクリーン感度)は30%と報告されている

免疫法の精度に関しては健常者コホートにおいて全例に内視鏡検査と免疫法FOBTを行い，免疫法FOBTのスクリーン感度は1日法56～67%，2日法77～83%，3日法89%[2]，特異度は97～98%と報告されている．化学法と免疫法を同時に行って比較した研究では免疫法の感度が高いと報告されている[5]．また一般の人口集団のランダム割付により免疫法と化学法を行う群に分けて，受容度(受診率)の影響も含めてadvanced adenomaとがんの発見率を比較した研究で，免疫法群で受診率，発見率，陽性反応適中度が高く，化学法より優れていることが明確に示された[6]．免疫法は化学法に替わるべき検診法として各国で導入が始まっている．

d）便潜血検査の検診間隔と対象年齢に関する証拠(表2, 3)

化学法のRCTにより検診間隔は2年まで死亡率減少効果が確定している．なおミネソタ研究では1年間隔では33%，2年間隔では20%の低下であり，罹患の減少も含め，1年間隔でより効果が高いことが示されている．免疫法では2年間隔で行われた研究もあり，化学法のエビデンスと合わせ2年間は有効性が認められたといえる．海外では2年間隔の検診を推奨する国が多い．

有効性のある年齢については，RCTではおもに45～74歳を対象としている(表3)．この年代についてもっとも強い証拠があるといえる．わが国では対象年齢に上限はないが世界的には年齢上限を定めており，精検の内視鏡の前処置など負担が大きいので高齢者には不利益が懸念され，わが国でも今後，設定すべきと考えられる．

2．内視鏡による検診(表4)

a）S状結腸内視鏡検査　有効性の証拠のレベル

以前から症例対照研究2研究により硬性S状結腸内視鏡(RS)による検診のRSが届く直腸・

表4 大腸内視鏡検診の有効性に関する主な証拠

年	研究者	Journal	研究デザイン	スクリーニング法	RR(95%CI) 罹患	RR(95%CI) 死亡
2010	Atkin	Lancet Oncol	RCT	Sigmoidoscopy	全大腸 0.77(0.70-0.84) Distal 0.64(0.57-0.72)	全大腸 0.69(0.59-0.82)
2011	Segnan	JNCI	RCT	Sigmoidoscopy	全大腸 0.82(0.69-0.96) Distal 0.76(0.62-0.94) Proximal 0.91(0.69-1.20)	全大腸がん 0.78(0.56-1.08) Distal 0.73(0.47-1.12) Proximal 0.85(0.52-1.39)
2012	Schoen	NEJM	RCT	Sigmoidoscopy*	全大腸 0.79(0.72-0.85) Distal 0.71(0.64-0.80) Proximal 0.86(0.76～0.97)	全大腸 0.74(0.63-0.87) Distal 0.50(0.38-0.64) Proximal 0.97(0.77～1.22)
2014	Holme	JAMA	RCT	Sigmoidoscopy/ sigmoidoscopy＋FOBT	全大腸 0.80(0.70-0.92)	全大腸 0.73(0.56-0.94)
2008	Baxter	Ann Intern Med	CCS	Colonoscopy	/	全大腸 0.69(0.63-0.74) Left-Sided 0.39(0.34-0.45) Right-Sided 1.07(0.94.1.21)
2013	Doubeni	Ann Intern Med	CCS	Colonoscopy	0.29(0.15-0.58) Right- sided 0.36(0.16-0.80) Left-sided 0.26(0.06-1.11) (進行がん罹患率)	/
2013	Nishihara	NEJM	Cohort	Colonoscopy	全大腸 0.44(0.38-0.52) Distal 0.24(0.18-0.32) Proximal0.72(0.57-0.92	全大腸 0.32(0.24-0.45) Distal 0.18(0.10-0.31) Proximal 0.47(0.29-0.76)

S状結腸がん死亡率のリスク低下が示唆されていたが，最近，Flexible Sigmoidoscopy(以下 Sigmoidoscopy)を1回だけ行う検診の有効性評価の大規模RCT 3研究と，3～5年間隔で行う1研究が報告された．これら質の高いRCTのうち，2研究において26～31%の死亡率減少効果が示され，3研究において18～23%の罹患率減少効果が示されている．英国の研究では罹患率減少効果は10年に渡って認められ，効果は長期間持続すると考えられる．

b）全大腸内視鏡検査(CS)

全大腸内視鏡検査(colonoscopy:CS)の有効性に関する質の高い研究はなかったが，比較的最近になってようやく中等度程度の質の症例対照研究などが報告され，死亡率減少効果が示唆されていた．これらの研究ではCSのスクリーニングは左側の大腸がんのリスク低下には寄与するが，右側の結腸がんのリスクは低下させないことが示唆されている．一方，最近報告されたコホート研究は非常に質の高いもので，大腸内視鏡検診受診が68%大腸がん死亡リスクを下げたことが報告された．とりわけ直腸，S状結腸がんではリスク低下は82%と効果は大きかった．この研究では右側結腸がんのリスクも低下する結果であるが，リスク低下の程度は左側に比べ小さかった．これらの結果は左側と右側で大腸がんのbiologyが異なることや，CSの感度が右側のがんに対して低いことなどを示唆する．

c）CSによる検診の不利益

CSを将来，対策型検診として検討する際に必要な不利益のデータについては，前投薬や下剤による前処置について死亡例が報告されている．CS自体による偶発症は1998年から2002年までの約300万例の検査で0.069%(2,038例)，死亡は0.00088%(26例)と高くはないとも言えるが，これらの報告は，大規模専門施設からのものであるため，実際より過小評価の可能性が高い．海外では詳しく客観性の高い調査報告があり，大腸穿孔の頻度の報告値はscreening CSについておよそ0.1～0.3%と日本より高い．

d）内視鏡検診のエビデンスの位置づけ

Sigmoidoscopyのエビデンスは確立し，CSの有効性も確実と考えられる．しかし，将来の対策型検診への導入には大腸穿孔など主要な不利益の実態把握が不可欠である．さらに深部結腸がんのリスクについて遠位のがんより効果が低い可能性が指摘されており，今後の研究課題である．またCSの処理能力は精検法に限っても必ずしも十分ではなく，現状では専門施設においての実施にとどまる．ただし，他のがん検診とは異なり，唯一，推奨できる任意型検診法であり，FOBTによる定期的な検診に加え，50～60代で一度行うことは積極的に勧められる．

3．その他―CT―colonography(3D-CT)

死亡率をエンドポイントとした研究はない．海外でNational CT colonography Trial(米国ACRIN研究　2007)など，腺腫の診断能を見たいくつかの前向き研究があり，大きな腺腫については内視鏡の感度とそれほど差がないとされる．しかし日本で行われている3D-CTについての研究報告はまだない．日本では画像表示法や前処置，糞便の画像処理のための造影剤が異なるのでその評価が別途必要である．とはいえ，海外の方法については精検法としては一定の評価は得られたと言える．

スクリーニング後の治療やフォローアップなどに関連するエビデンス

1．ポリープ切除の効果[7]

FOBTの検診で検診を提供された群において大腸がん罹患率が減少するエビデンスが示されているが，その要因は頻繁に行われるポリペクトミーであるとされてきた．米国National polyp studyの長期観察から，ポリペクトミーが大腸ポリープ患者の大腸がん死亡リスクを減少させる効果も示された．これらから大腸がん検診の効果は大腸がんの早期発見のみならず，ポリープ切除の効果にもよることが強く示唆される．

2．ポリープ切除後，大腸内視鏡後の大腸がんや腺腫のリスク[8,9]

検診では便潜血検査陽性者の30～40%に大腸ポリープが発見され，その一部が切除の対象となる．また従来，ポリープ切除後の患者は基本的には内視鏡でフォローアップされるが，1年毎のフォローアップなど頻繁な内視鏡検査が行われてきた．この方針に関連するエビデンスとしては，初回内視鏡の所見別にリスクが異なり，腺腫なし，6 mm未満の腺腫のみあり，6 mm以上の腺腫あり，粘膜内がんありで10 mm以上の腺腫あるいは粘膜内がんのリスクが高くなり，初回腺腫なしでは1年後のリスクは0.1%にとどまることが後ろ向き研究ながら報告されている．

RCTであるNational polyp studyにおいて，切除後3年でのフォローと1，3年後のフォローでは浸潤がんのリスクに差はないと示されたことは重要なエビデンスである．まだ最終結果として論文にはなっていないがわが国のJapan polyp studyからも同様の結果が得られているという．これらにより，切除後3年間は毎年のフォローに比べ浸潤がんのリスクは上昇しないことが示されたといえる．またコホート研究により，初回，腺腫がない場合には5年間，浸潤がんリスクは上昇しないことも示唆されている．さらにsigmoidoscopyに関するRCTでは，1回行った群で対照群に比べ10年間罹患率(浸潤がんの)が有意に低下することが示され，これまでの症例対照研究と合わせ，内視鏡検診の効果は長期にわたって持続することも明らかとなったと言える．フォローアップの間隔年数としては，浸潤がんのリスクが上昇しない期間の最大値が基準となることから，従来のような短期間でのフォローアップは必要はないと考えられる．

以上から，ごく一部の非常にハイリスクな症例を除けば切除後3年以上は開けられること，その後はFOBTの検診に戻すことが合理的と考えられる．そのようなリスク要因についてより

詳細な根拠を得るために，内視鏡によるフォローの間隔とリスクに関する研究の重要度は高い．また，前述のように右側がんに対する内視鏡後のリスクが左側がんとは異なる可能性についても研究課題として注目される．

今後行うべきこと―日本で大腸がん検診の成果をあげるために

大腸がん検診はきちんと行うことで，その死亡率を国レベルで低下させる成果が十分期待できる．海外，特に欧州を中心に，乳がんと子宮がん検診で国レベルの死亡率を減少させた仕組みは組織型検診という方法であり，その骨子は科学的根拠のある検診を徹底的に精度管理して行うというものである[4]．わが国ではこれまでがん検診の成果があがっていないが，それはこの組織型検診の条件から逸脱している状況に原因がある．がん検診全般に精度管理の基盤を作らずにやりっ放しの検診が横行している状況である．大腸がん検診はその科学的根拠が確立しており，精度管理がポイントになる．そもそも，精度管理の体制ができていなければ検診は行うべきではないというのが検診の原則であり，それが組織型検診の背景である．日本はまだ成果をあげられる水準まで検診の理解が進んでいないのである．

文　献

1) 厚生労働省人口動態統計．
2) 斎藤　博，他：死亡率低下を目指した大腸がん検診の将来像．日本臨牀 72:15-21，2014
3) 斎藤　博，他：大腸がん検診のエビデンスと今後の研究の展望．日消誌 111:453-463，2014
4) 斎藤　博，他：がん治療エッセンシャルガイド．南山堂，190-197，2012
5) 斎藤　博：大腸癌検診の発見率，偽陰性率はどのくらいですか？　大腸癌 FRONTIER 2:94-97，2009
6) Van Rossum LG, et al.: Random comparison of guaiac and immunochemical fecal occult blood test for colorectal cancer in a screening population. Gastroenterology 136: 82-90, 2008
7) Winawer SJ, et al.: Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. N Engl J Med 328: 901-906, 1993
8) Imperiale TF, et al.: Five-year risk of colorectal neoplasia after negative screening colonoscopy. N Engl J Med 359: 1218-1224, 2008
9) Matsuda T, et al.: Five-year incidence of advanced neoplasia after initial colonoscopy in Japan: a multicenter retrospective cohort study. Jpn J Clin Oncol 39: 434-442, 2009

著者連絡先（〒104-0045）　東京都中央区築地 5-1-1
国立がん研究センターがん予防・検診研究センター検診研究部　斎藤　博

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2014;44(5)513–514

Cancer Statistics Digest

Five-year Relative Survival Rate of Uterus Cancer in the USA, Europe and Japan

In order to compare survival rates in Japan with those in the USA and European countries, we abstracted the 5-year relative survival rate from several data sources. Survival rates of cancer diagnosed in 1995–99 in the USA were abstracted from 18 cancer registries in the Surveillance Epidemiology and End Results (SEER) data (1). Survival rates of cancer diagnosed in 1995–99 in the UK and Norway were from four cancer registries (Norway, the UK: Northern Ireland, the UK: Scotland and the UK: Wales) in the European Network of Cancer Registries (ENCR) data (2), and the rate of cancer diagnosed in 2000–2002 in Japan was reported from six cancer registries (Miyagi, Yamagata, Niigata, Fukui, Osaka, and Nagasaki) in the Monitoring of Cancer Incidence in Japan (MCIJ) project (3). Here, we compared the survival rate of cervix uteri cancer coded as C53 and corpus uteri cancer coded as C54 (ICD10). Figures 1 and 2 show the 5-year relative survival rate of cervix and corpus uteri cancer by age category, respectively.

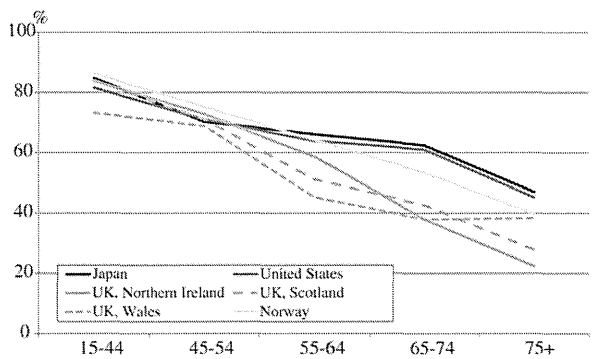

Figure 1. Five-year relative survival rate of cervix uteri cancer. Japan: Monitoring of Cancer Incidence in Japan (MCIJ) (ICD:C53). The United States: SEER 18 Registries (ICD:C53). The UK and Norway: European Network of Cancer Registries (ENCR) (ICD:C53).

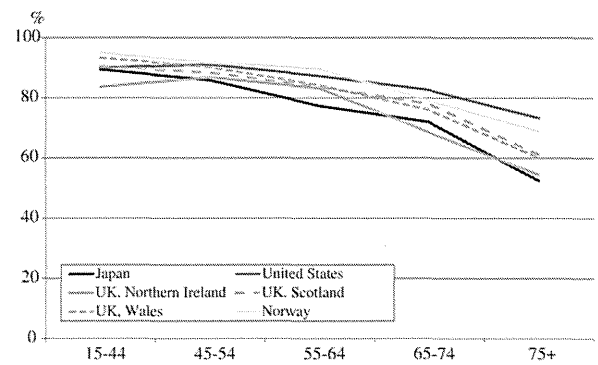

Figure 2. Five-year relative survival rate of corpus uteri cancer. Japan: Monitoring of Cancer Incidence in Japan (MCIJ) (ICD:C54). The United States: SEER 18 Registries (ICD:C54). The UK and Norway: European Network of Cancer Registries (ENCR) (ICD:C54).

For cervix uteri cancer, the 5-year relative survival rates for those 15–44 years old were around 80% and decreased with age. The rates in Japan and the USA were relatively high for those over 65 years old and rates in all the areas in the UK were low. In the USA and Japan, 5-year relative survival rates for those aged over 75 years old were 45–47% whereas in the UK (Scotland and Northern Ireland), the rates were under 30%.

For corpus uteri cancer, the 5-year relative survival rates were higher than those for cervix uteri cancer in all age groups. The rates for those aged 15–44 years old were 73–86% and decreased with age. The rates in the USA and Norway were relatively high and about 70% even in those over 75 years old. In Japan, the rates in old age groups were the highest for cervix uteri cancer whereas were as low as those in the UK, Northern Ireland.

Kumiko Saika and Ryoko Machii
Division of Screening Assessment and Management,
Research Center for Cancer Prevention and Screening, National Cancer Center
doi:10.1093/jjco/hyu055

References

1. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data+Hurricane Katrina Impacted Louisiana Cases, Nov 2012 Sub (1973–2010) - Linked To County Attributes - Total U.S., 1969–2011 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission.

2. Steliarova-Foucher E, O'Callaghan M, Ferlay J, Masuyer E, Forman D, Comber H, Bray F: European Cancer Observatory: Cancer Incidence, Mortality, Prevalence and Survival in Europe. Version 1.0 (September 2012) European Network of Cancer Registries, International Agency for Research on Cancer. Available from http://eco.iarc.fr, accessed on 08/10/2013.
3. Matsuda T, Ajiki W, Marugame T, Ioka A, Tsukuma H, Sobue T; Research Group of Population-Based Cancer Registries of Japan. Monitoring of Cancer Incidence in Japan - Survival 2003–2005 Report (Center for Cancer Control and Information Services, National Cancer Center, 2013) Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: a chronological and international comparative study. *Jpn J Clin Oncol* 2011;41:40–51.

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2014;44(7)704

Cancer Statistics Digest

Five-year Relative Survival Rate of Gallbladder Cancer in the USA, Europe and Japan

In order to compare survival rates in Japan with those in the USA and European countries, we abstracted the 5-year relative survival rate from several data sources. Survival rates of cancer diagnosed in 1995–99 in the USA were abstracted from 18 cancer registries in the Surveillance Epidemiology and End Results (SEER) data (1). Survival rates of cancer diagnosed in 1995–99 in the UK and Norway were from four cancer registries (Norway, the UK: Northern Ireland, the UK: Scotland and the UK: Wales) in the European Network of Cancer Registries (ENCR) data (2), and the rate of cancer diagnosed in 2000–2002 in Japan was reported from six cancer registries (Miyagi, Yamagata, Niigata, Fukui, Osaka, and Nagasaki) in the Monitoring of Cancer Incidence in Japan (MCIJ) project (3). Here, we compared the survival rate of gallbladder and other biliary cancer coded as C23–C24 (ICD10). Figure 1 shows the 5-year relative survival rate of gallbladder and other biliary cancer by age category for males; Fig. 2 shows these data for females.

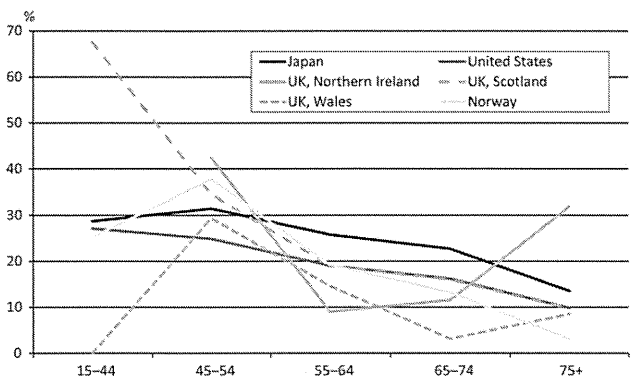

Figure 1. Five-year relative survival rate of gallbladder cancer (males). Japan: Monitoring of Cancer Incidence in Japan (MCIJ) (ICD:C23–C24). The United States: SEER 18 Registries (ICD:C23–C24). The UK and Norway: European Network of Cancer Registries (ENCR) (ICD:C23–C24).

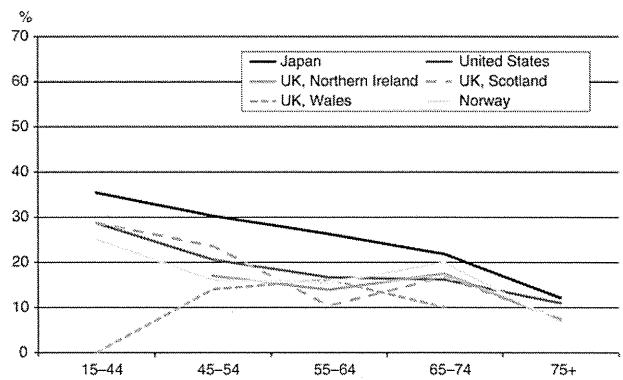

Figure 2. Five-year relative survival rate of gallbladder cancer (females). Japan: Monitoring of Cancer Incidence in Japan (MCIJ) (ICD:C23–C24). The United States: SEER 18 Registries (ICD:C23–C24). The UK and Norway: European Network of Cancer Registries (ENCR) (ICD:C23–C24).

The 5-year relative survival rate of gallbladder cancer was decreasing with age; however, the age differences were not so large compared with other cancer sites. This is because the rates in those below 55 years old were relatively lower than those of other cancer sites. The rates were between 10 and 30% for males, and between 10 and 20% for females. In Japan, the rates tend to be high in all age categories, and in the USA and European areas, the rates were similar.

Kumiko Saika and Ryoko Machii
Division of Screening Assessment and Management,
Research Center for Cancer Prevention and Screening, National Cancer Center
doi:10.1093/jjco/hyu087

References

1. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data+Hurricane Katrina Impacted Louisiana Cases, Nov 2012 Sub (1973–2010) - Linked To County Attributes - Total U.S., 1969–2011 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission.
2. Steliarova-Foucher E, O'Callaghan M, Ferlay J, Masuyer E, Forman D, Comber H, Bray F: European Cancer Observatory: Cancer Incidence, Mortality, Prevalence and Survival in Europe. Version 1.0 (September 2012) European Network of Cancer Registries, International Agency for Research on Cancer. Available from http://eco.iarc.fr, accessed on 08/10/2013.
3. Matsuda T, Ajiki W, Marugame T, Ioka A, Tsukuma H, Sobue T; Research Group of Population-Based Cancer Registries of Japan. Monitoring of Cancer Incidence in Japan - Survival 2003–005 Report (Center for Cancer Control and Information Services, National Cancer Center, 2013) Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: a chronological and international comparative study. *Jpn J Clin Oncol* 2011;41:40–51.

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2014;44(10)1015–1016

Cancer Statistics Digest

Five-year Relative Survival Rate of Larynx Cancer in the USA, Europe and Japan

In order to compare survival rates in Japan with those in the USA and European countries, we abstracted the 5-year relative survival rate from several data sources. Survival rates of cancer diagnosed in 1995–99 in the USA were abstracted from 18 cancer registries in the Surveillance Epidemiology and End Results (SEER) data (1). Survival rates of cancer diagnosed in 1995–99 in the UK and Norway were from four cancer registries (Norway, the UK: Northern Ireland, the UK: Scotland and the UK: Wales) in the European Network of Cancer Registries (ENCR) data (2), and the rate of cancer diagnosed in 2000–2002 in Japan was reported from six cancer registries (Miyagi, Yamagata, Niigata, Fukui, Osaka, and Nagasaki) in the Monitoring of Cancer Incidence in Japan (MCIJ) project (3). Here, we compared the cancer survival rate for larynx coded as C32 (ICD10). Figure 1 shows the 5-year relative survival rate of larynx cancer by age category for males; Fig. 2 shows these data for females. In these figures, even if the 5-year relative survival rate was over 100%, the rate was shown as it was.

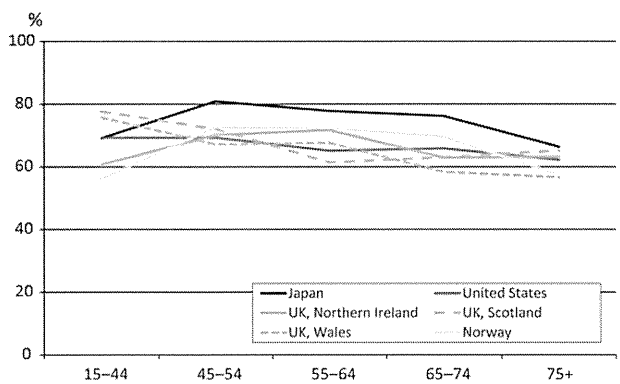

Figure 1. Five-year relative survival rate of larynx cancer (males). Japan: Monitoring of Cancer Incidence in Japan (MCIJ) (ICD:C32). The United States: SEER 18 Registries (ICD:C32). The UK and Norway: European Network of Cancer Registries (ENCR) (ICD:C32).

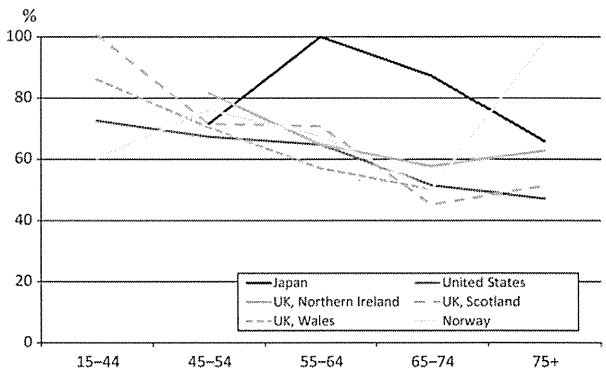

Figure 2. Five-year relative survival rate of larynx cancer (females). Japan: Monitoring of Cancer Incidence in Japan (MCIJ) (ICD:C32). The United States: SEER 18 Registries (ICD:C32). The UK and Norway: European Network of Cancer Registries (ENCR) (ICD:C32).

The survival rates for males are in the range from 60 to 80% for all age categories. In Japan, the rates are the highest in almost all age groups. In the USA and the UK (Scotland and Wales), survival rates are the highest in the youngest age category and they decrease with age afterwards. The degree of the decrease in survival rate with age in the USA is a little smaller than those in the UK, and is almost constant especially after 55–64 years old. The rates in Japan, Norway, and Northern Ireland show a similar trend. Those in the former two countries are the highest in those aged 45–54 years, and that in Northern Ireland is the highest in those aged 55–64 years. Survival rates in these three countries decrease gently after these peaks.

The survival rates for females are in the range from 40 to 100%. Since the incident rates of larynx cancer among females are considerably low (4), the relative survival rates in Japan and UK exceed 100% and the age trends are not smooth. However, it seems to be clear that the survival rate in Japan is higher than those in other countries, and that the survival rate in the advanced age group tends to be lower.

Ryoko Machii and Kumiko Saika
Division of Screening Assessment and Management,
Research Center for Cancer Prevention and Screening,
National Cancer Center
doi:10.1093/jjco/hyu147

References

1. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data+Hurricane Katrina Impacted Louisiana Cases, Nov 2012 Sub (1973–2010) - Linked To County Attributes - Total U.S., 1969–2011 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission.
2. Steliarova-Foucher E, O'Callaghan M, Ferlay J, Masuyer E, Forman D, Comber H, Bray F: European Cancer Observatory: Cancer Incidence, Mortality, Prevalence and Survival in Europe. Version 1.0 (September 2012) European Network of Cancer Registries, International Agency for Research on Cancer. Available from http://eco.iarc.fr, accessed on 08/10/2013.
3. Matsuda T, Ajiki W, Marugame T, Ioka A, Tsukuma H, Sobue T; Research Group of Population-Based Cancer Registries of Japan. Monitoring of Cancer Incidence in Japan - Survival 2003–2005 Report (Center for Cancer Control and Information Services, National Cancer Center, 2013) Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: a chronological and international comparative study. Jpn J Clin Oncol *2011; 41*: 40–51.
4. Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014. Available from: http://ci5.iarc.fr.