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ORIGINAL ARTICLE

A nation-wide survey of follow-up strategies for esophageal cancer patients after a curative esophagectomy or a complete response by definitive chemoradiotherapy in Japan

Yasushi Toh[1] · Yuko Kitagawa[2] · Hiroyuki Kuwano[3] · Motoyasu Kusano[4] · Tsuneo Oyama[5] · Manabu Muto[6] · Hiroyuki Kato[7] · Hiroya Takeuchi[2] · Yuichiro Doki[8] · Yoshio Naomoto[9] · Kenji Nemoto[10] · Hisahiro Matsubara[11] · Tatsuya Miyazaki[3] · Akio Yanagisawa[12] · Takashi Uno[13] · Ken Kato[14] · Masahiro Yoshida[15] · Hirofumi Kawakubo[2] · Eisuke Booka[2]

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Abstract

Background There is a lack of critical evidence to justify the methods of follow-up after a curative esophagectomy or a complete response to definitive chemoradiotherapy (dCRT). Consequently, a wide variety of practices are in place throughout the world.

Methods A questionnaire concerning follow-up protocols was sent via electronic email for a nation-wide survey of the 117 Japanese hospitals that are recognized by the Japan Esophageal Society as training facilities for certified esophageal surgeons. Seventy-seven hospitals responded to the questionnaire.

Results Most hospitals follow their patients for at least 5 years after esophagectomy or dCRT, usually at a frequency of more than 4 times per year with clinical visits and physical examinations in the 1st and 2nd year after treatment. About 65–75 and 40 % of the hospitals continue the follow-up until the 7th and 10th year after treatment, respectively. Most hospitals measure CEA and SCC-Ag and almost all hospitals utilize CT scans of the cervix, chest and abdomen for the follow-up. Most of the hospitals reported performing an upper gastrointestinal endoscopy at least once per year until the 5th year after treatment, more frequently for post-dCRT patients than for post-esophagectomy patients. Other imaging modalities such as FDG-PET/

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✉ Yasushi Toh
ytoh@nk-cc.go.jp

[1] Department of Gastroenterological Surgery, National Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka 811-1395, Japan

[2] Department of Surgery, Keio University School of Medicine, Tokyo, Japan

[3] Department of General Surgical Science, Gunma University Graduate School of Medicine, Gunma, Japan

[4] Department of Endoscopy and Endoscopic Surgery, Gunma University Hospital, Gunma, Japan

[5] Department of Endoscopy, Saku Central Hospital Advanced Care Center, Nagano, Japan

[6] Department of Therapeutic Oncology, Kyoto University Graduate School of Medicine, Kyoto, Japan

[7] Department of Surgery 1, Dokkyo Medical University, Tochigi, Japan

[8] Division of Gastroenterological Surgery, Department of Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan

[9] Department of General Surgery, Kawasaki Medical School, Okayama, Japan

[10] Department of Radiation Oncology, Yamagata University School of Medicine, Yamagata, Japan

[11] Department of Frontier Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan

[12] Department of Pathology, Kyoto Prefectural University of Medicine, Kyoto, Japan

[13] Department of Radiology, Graduate School of Medicine, Chiba University, Chiba, Japan

[14] Gastrointestinal Oncology Division, National Cancer Center, Tokyo, Japan

[15] Department of Hemodialysis and Surgery, Chemotherapy Research Institute, International University of Health and Welfare, Ichikawa, Japan

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CT, cervical and abdominal USs, and chest and abdominal X-rays were incorporated at much lower rates.
Conclusions Follow-up protocols for patients who have been treated for esophageal cancer with curative intent vary among the hospitals in Japan. Based on these data, the most popular follow-up protocols in Japan are shown.

Keywords Esophageal cancer · Curative esophagectomy · Definitive chemoradiation · Recurrence · Follow-up strategies · Nation-wide survey

Abbreviations

dCRT	Definitive chemoradiotherapy
CR	Complete response
QOL	Quality of life
CV	Clinical visit
CT	Computed tomography
CEA	Carcinoembryonic antigen
SCC-Ag	Squamous cell carcinoma antigen
p53-Ab	p53 antibody
FDG-PET	Positron emission tomography with ^{18}F-fluorodeoxyglucose
UGIE	Upper gastrointestinal endoscopy
US	Ultrasonography
Xp	Plain X-ray

Introduction

Despite the recent improvements in the treatment outcome of esophageal cancer patients who are treated with multimodality therapies including esophagectomy with lymph node dissection or definitive chemoradiotherapy (dCRT), post-treatment recurrence occurs in a considerable number of patients [1–4]. Curative treatments of recurrence are necessary to further improve the prognosis of patients after such treatments with curative intent, although achieving a successful cure in patients with recurrence remains rare, even after multimodality therapies. However, critical evidence to justify the treatment strategies for cases of recurrence and the methods of follow-up to diagnose recurrence after the initial treatment with curative intent is still lacking in Japan [5] and Western countries [6–8]; consequently, a wide variety of practices are in place throughout the world.

The primary aim of follow-up after a curative resection of esophageal cancer or obtaining a complete response (CR) by dCRT is to detect local recurrence, distant metastases or metachronous primary cancers at an early stage when curative treatments are still possible, thus leading to an improvement of the prognosis. Follow-up is also important for evaluating and managing the patient's general status and quality of life (QOL), because esophagectomy and dCRT are associated with a significant level of postoperative complications and late toxicities, such as pleural or pericardial effusion [9]. The following questions should be considered when determining follow-up protocols after treatments with curative intent for esophageal cancer: (1) what is the best combination of modalities for diagnosing recurrences at an early stage? (2) Does the early detection of recurrence lead to the elongation of survival or QOL improvement? (3) What methods are the most effective from an economical point of view?

Several recommendations for follow-up after a curative resection or dCRT for esophageal cancer are noted in the guidelines of the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), although no references that show evidence are cited [10, 11]. Large-scale clinical trials that address follow-up methods after esophageal cancer treatment seem difficult to design, because the choice of the initial treatment varies markedly, depending on the stage of the disease and the patient's general condition at the time of diagnosis. Instead, large-scale data collection based on some form of consensus protocol(s) might answer the above-mentioned questions. At present, however, consensus follow-up protocols are still a long way from being established. Moreover, it appears to be hard to directly adapt the data from the Western countries to the Japanese patients with esophageal cancer, because there are considerable differences in the predominant histology and tumor locations, the surgical methods used and the survival rates after surgery between patients in Japan and those in the Western countries [12].

The aims of the present study are to investigate the current follow-up practices after treatments with curative intent for patients with esophageal cancer using a nation-wide survey in Japan and to attempt to create a consensus follow-up protocol.

Materials and methods

In October 2014, a questionnaire was sent via electric mail, as a nation-wide survey of 117 hospitals that are recognized by the Japan Esophageal Society (JES) as training facilities for certifying specialized esophageal surgeons. By December 15, 2014, answers were obtained from 77 hospitals (65.8 %) (Online Resource 1).

The questionnaire included the numbers of hospital beds, newly registered esophageal cancer patients per year and certified esophageal surgeons. Online Resource 2 shows the backgrounds of the hospitals that responded to the questionnaire. Sixty-seven (88.2 %) of the hospitals have more than 500 beds (Online Resource 2A). Online Resources 2B and 2C show the numbers of esophageal cancer patients per year and JES-certified esophageal surgeons in each hospital, respectively. At the time of the survey there were 207 JES-certified esophageal surgeons in Japan.

In Japan, dCRT was conducted by surgeons, radiation oncologists and either of them in 43, 39 and 18 %, respectively. The follow-up after dCRT was done in a similar proportion. Anti-cancer chemotherapy was performed by surgeons or medical oncologists in 52 or 25 % of the hospitals, respectively. Terminal care is also given by surgeons in 44 % of the hospitals in Japan (Online Resource 3).

The modalities used for follow-up after a curative esophagectomy or CR by dCRT in each hospital were investigated, these included: clinical visits (CVs) for anamnesis and physical examination, tumor markers (carcinoembryonic antigen: CEA, squamous cell cancer antigen: SCC-Ag, others), chest plain X-ray (Xp), abdominal Xp, cervical-chest and abdominal-pelvic computed tomography (CT), cervical ultrasound (US), abdominal US, positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET), bone scintigraphy, upper gastrointestinal endoscopy (UGIE), colonoscopy or colonography, screening of head and neck (H&N) region and the assessment of QOL. The frequency and duration of each modality were investigated for 10 years after the initial treatment.

The protocols for the patients with Stage 0/I and Stage II/III/IV (pathological stages for esophagectomy and clinical stages for dCRT) [13, 14] were separately assessed for each of curative esophagectomy and dCRT, because there are apparent differences in the survival rates between Stage I and Stage II in Japan [15].

Results

Seventy-seven hospitals responded to the questions on post-esophagectomy protocols and 73 responded to the questions on post-dCRT protocols. Thirty-five (44.5 %) of 77, and 35 (47.9 %) of 73 hospitals reported that they utilized the same follow-up protocols after esophagectomy or dCRT, respectively, regardless of stage.

Clinical visits for anamnesis and physical examination

The frequencies of CVs for anamnesis and physical examination in the subsequent years after esophagectomy and dCRT are shown in Fig. 1. Most of the hospitals reported that they followed their patients more than 4 times in the 1st year after either treatment. Seventy-four percent and 68 % of the hospitals reported that they performed CVs for patients with Stage II/III/IV at least 4 times a year, even in the 3rd year, after esophagectomy and dCRT, respectively. All hospitals continued CVs for all stages until the 5th year after treatment. Even in the 5th year, most hospitals followed the patients of any stage at least twice a year. Roughly speaking, one-fourth of the hospitals reported that they terminated their follow-ups after 5 years, while about 40 % reported that they performed a CV once or twice a year until the 10th year, after either treatment. For the patients of Stage 0/I, CVs were performed slightly less frequently (for both treatments) in the first 5 years than those for Stage II/III/IV (Fig. 1).

Measurements of tumor markers

Nearly all of the hospitals reported that they measured CEA and SCC-Ag for at least 5 years after treatments with curative intent (Online Resource 4). These markers were mostly measured at the same time. With the exception of the 1st year, the frequency and duration of the measurements were similar (Online Resources 5 and 6).

Other than CEA and SCC-Ag, cyfra (cytokeratin 19 fragment), p53 antibody (p53-Ab) and CA19-9 were incorporated in the follow-up protocols of some of the hospitals (Online Resource 4). When incorporated, the frequencies of measurement were similar to the frequencies of measurement of CEA and SCC-Ag (data not shown).

Routine imaging modalities

Ninety-four percent of the hospitals reported that they utilized CT scans ranging from the cervix to the pelvis (or sometimes of the upper abdomen instead) in their follow-up protocols after treatments with curative intent (Fig. 2; Online Resource 7). In the 1st year after esophagectomy and dCRT, about 90 % of the hospitals reported performing CT at least twice, while 54 and 74 % reported performing CT 3 or 4 times a year for Stage II/III/IV after esophagectomy and dCRT, respectively. Eighty-seven percent and 92 % of the hospitals performed CT for Stage II/III/IV more than twice a year even in the 3rd year after esophagectomy and dCRT, respectively. Most hospitals continued performing CT scans until the 5th year. Roughly speaking, about 60 and 30 % of the hospitals continued performing CT scans for Stage II/III/IV patients until the 7th and 10th years after treatment, respectively. The post-dCRT follow-up seemed to be more intensive than the post-esophagectomy follow-up during the 5-year period. A small number of the hospitals, most of which incorporated FDG-PET in their protocols, did not utilize CTs (data not shown). Including these hospitals, 20–30 % reported that they utilized FDG-PET/CT examinations for follow-up at least 5 years after treatment (Online Resource 8).

Chest Xp was only utilized in only the 1st year after esophagectomy and dCRT for Stage II/III/IV patients in 32 and 21 % of the hospitals, respectively; and in only 5–10 % in the 2nd year and thereafter. Abdominal Xp was performed less frequently. Cervical and abdominal USs were incorporated in 11–13 and 14–18 of the hospitals, respectively, for 5 years. Bone metastasis was investigated using bone scintigraphy in only 5–7 % (data not shown).

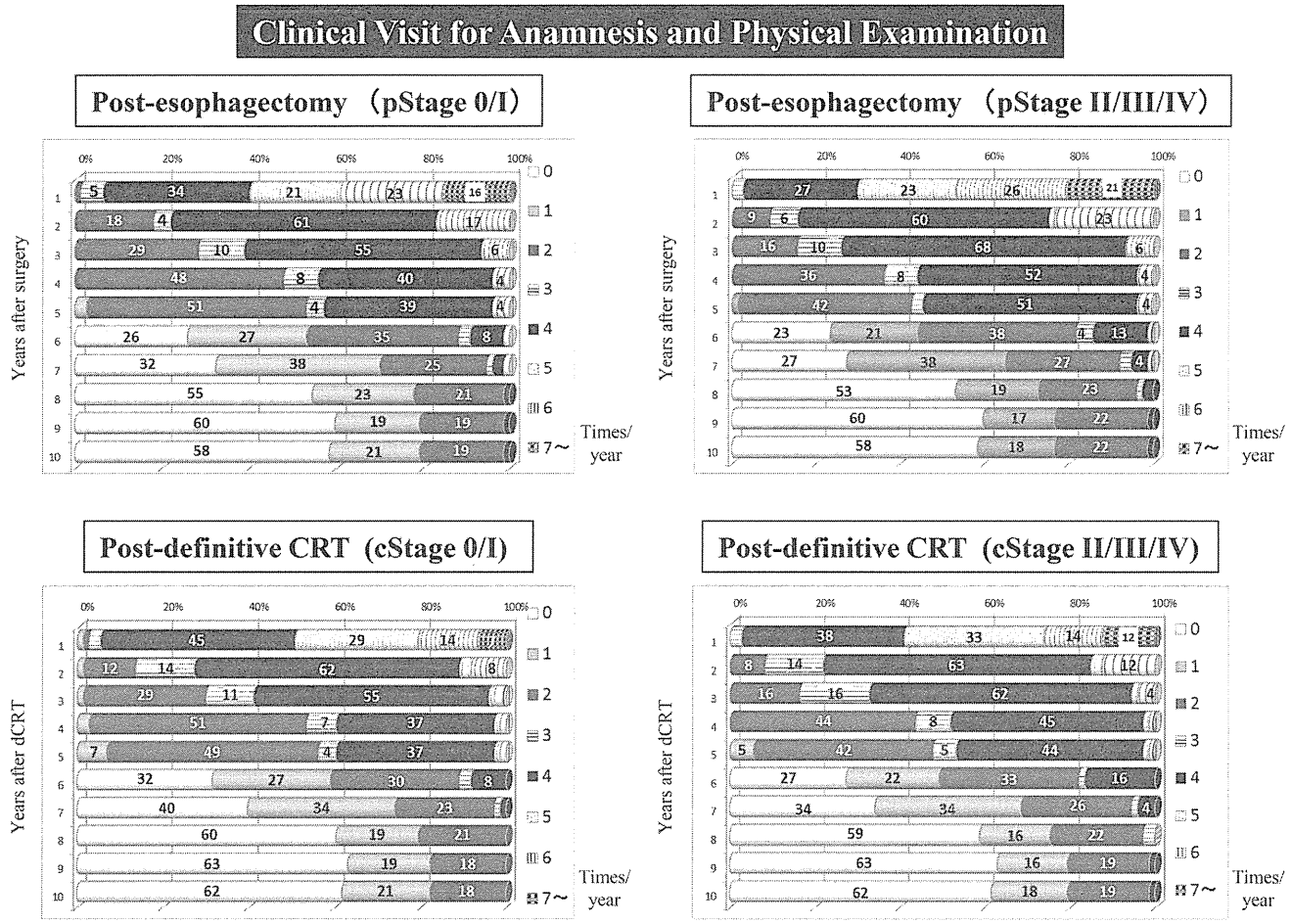

Fig. 1 The frequencies per year and duration after treatments with curative intent concerning "clinical visits for anamnesis and physical examination" after esophagectomy (pStage0/I and pStageII/III/IV) and definitive chemoradiotherapy (cStage0/I and cStageII/III/IV) are shown separately

Upper gastrointestinal endoscopy (UGIE)

The purpose of UGIE is to check for recurrences at the anastomotic sites after esophagectomy or at the primary lesions that responded completely to dCRT, for the occurrence of multiple metachronous cancers in the remnant esophagus and the conduits, including the stomach and the colon, and for the occurrence of gastro-esophageal reflux disease and anastomotic strictures.

For post-esophagectomy patients of any pStage, UGIE was performed once or twice a year in most hospitals for 5 years and was continued until the 7th and the 10th years in more than 70 and 40 % of the hospitals, respectively. For post-dCRT patients of any cStage, UGIE was performed much more frequently than for post-esophagectomy patients, possibly because the whole esophagus is preserved. In the 1st year after dCRT, approximately 50 % of the hospitals reported that they performed UGIE four times or more per year. UGIE was continued in nearly 100, 65 and 40 % of the hospitals until the 5th, 7th and the 10th years, respectively (Fig. 3).

Screening of metachronous multiple cancers in other organs

It is well known that esophageal cancers are frequently accompanied by metachronous cancers of other organs, especially of the H&N regions, stomach and colon [15]. The screening of H&N cancers by H&N surgeons and/or UGIE was performed once a year in only half of the hospitals for 5 years after both esophagectomy and dCRT, regardless of stage (Online Resource 9). The screening of colon cancers was performed bi-annually at approximately 20 % of the hospitals (Online Resource 10).

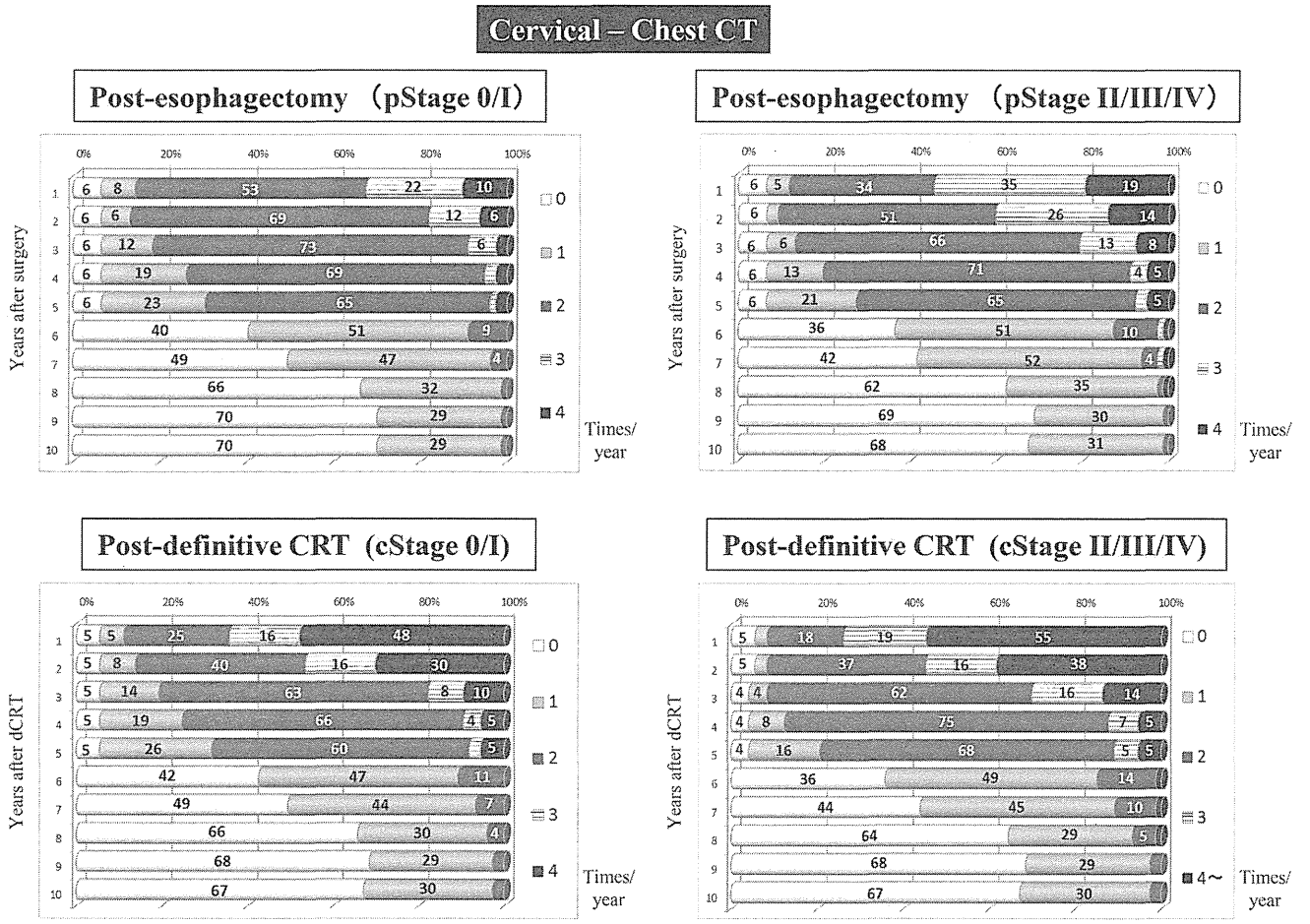

Fig. 2 The frequencies per year and duration after treatments with curative intent concerning "cervical to chest CT" after esophagectomy (pStage0/I and pStageII/III/IV) and definitive chemoradiotherapy (cStage0/I and cStageII/III/IV) are shown separately

Evaluation of post-treatment QOL

Only 7 and 6 hospitals evaluated the patient's QOL after esophagectomy and dCRT, respectively, using validated tools such as EORTC-OES18 and FACT-E [16, 17] (data not shown).

Discussion

It is obvious that some of the patients with recurrence after a curative esophagectomy or dCRT can be cured when they are diagnosed at an early stage by re-resection, radiotherapy or chemoradiotherapy [18–24]. Thus, it is important to find recurrences of esophageal cancers after a curative esophagectomy or dCRT at the earliest stage possible for the patients to be able to undertake further curative treatments before the tumor becomes unresectable and/or their general status deteriorates. Furthermore, the early detection of recurrence might achieve better compliance to various treatments and the opportunity to obtain a more prolonged survival and a better QOL. Abate et al. [1] showed that frequent early follow-up was appropriate after esophagectomy for adenocarcinoma and that survival after recurrence was improved by the therapies. On the other hand, there are some reports suggesting that an annual CT scan does not improve the clinical outcome after esophagectomy for esophageal cancer [6] and that intensive follow-up with routine imaging and endoscopy after surgery might not be justified for patients with gastro-esophageal cancers, especially in the light of the cost [8].

No standard, evidence-based method for follow-up observation after a curative esophagectomy or dCRT for esophageal cancer has ever been established [1, 5, 6]. In these circumstances, the follow-up protocols after esophagectomy or dCRT vary widely throughout the world and reflect institutional preferences [1, 5, 6]. At present, follow-up trends have not been investigated, even on a single-country basis. Thus, this nation-wide survey was conducted in order to clarify the present status of follow-up

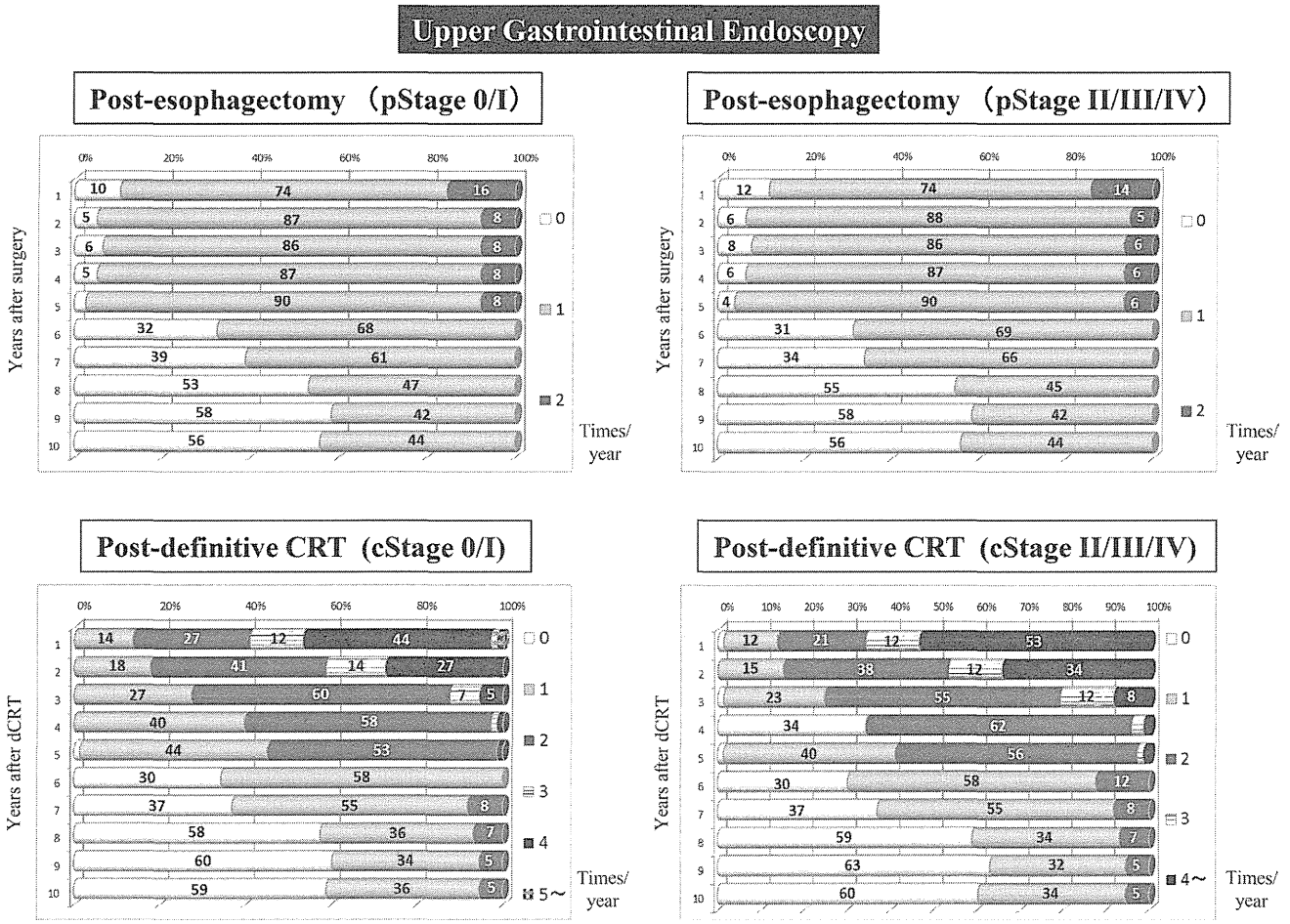

Fig. 3 The frequencies per year and duration after treatments with curative intent concerning "upper gastrointestinal endoscopy" after esophagectomy (pStage0/I and pStageII/III/IV) and definitive chemoradiotherapy (cStage0/I and cStageII/III/IV) are shown separately

protocols after esophagectomy or dCRT and, if possible, to reach a general agreement among Japanese hospitals.

With regard to the frequency and duration of follow-up, most hospitals follow their patients for 5 years after esophagectomy or dCRT, and at an especially high frequency in the first 3 years after treatment (Fig. 1). This seems to be reasonable, considering that most of the recurrences are reported to occur within 2 years after esophagectomy [5, 25, 26] and dCRT [4]. Moreover, about 70 and 40 % of the hospitals continue the follow-up until the 7th and 10th years after the treatments, respectively. This may be beneficial for checking for any changes of the patients' QOL, the occurrence of late toxicities due to dCRT [9], and for managing the patients' general conditions.

Almost all hospitals utilized a CT scan ranging from the cervix to the abdomen for follow-up (Fig. 2). Other imaging modalities such as FDG-PET/CT, cervical and abdominal USs, and chest and abdominal Xps were incorporated at much lower rates. UGIE was more frequently performed for post-dCRT patients than post-esophagectomy patients (Fig. 3). This is reasonable, because locoregional recurrence after dCRT occurs in 41 % of all patients, most frequently at the site of the primary tumor in the esophagus [4]. It is also necessary to check the development of either metachronous remnant esophageal cancer or multiple cancers of the H&N region, the stomach and the colon, because Sato et al. [27] reported that a second malignancy was the major cause of death among patients without any lymph node metastasis who underwent an esophagectomy for thoracic esophageal cancer. Oki et al. [28] reported that frequent endoscopic examinations were important even several years after performing an esophagectomy, since the risk of gastric tube cancer was higher than the risk of a recurrence of esophageal cancer several years after an esophagectomy and that only an early diagnosis permitted a less invasive and appropriate approach for the treatment of gastric tube cancer.

Although it is very difficult to establish a follow-up protocol with a nation-wide consensus, we dare to propose a follow-up protocol after curative esophagectomy and

Table 1 The most common modalities and their frequencies per year at participating hospitals during follow-up protocol after treatments with curative intent of esophageal cancer patients

	Year after treatment	1st		2nd		3rd		4th		5th		6th		7th		8th		9th		10th	
		Times/year	%	Times/year	%	Times/year	%	Times/year	%	Times/year	%	Times/year	%	Times/year	%	Times/year	%	Times/year	%	Times/year	%
Clinical visit																					
Post-esophagectomy	Most	4	27	4	60	4	68	4	52	4	51	2	38	1	38	0	53	0	60	0	58
	2nd most	6	26	6	23	2	16	2	36	2	42	0	23	0 or 2	27	2	23	2	22	2	22
Post-dCRT	Most	4	38	4	63	4	62	4	45	4	44	2	33	1 or 0	34	0	59	0	63	0	62
	2nd most	5	33	3	14	2 or 3	16	2	44	2	42	0	27	0 or 1	34	2	22	2	19	2	19
Tumor marker (CEA)[a]																					
Post-esophagectomy	Most	4	35	4	53	4	57	2	44	2	52	2	40	1	35	0	55	0	61	0	61
	2nd most	6	21	6	18	2	25	4	43	4	42	1	30	2	31	2	25	2	23	2	21
Post-dCRT	Most	4	38	4	56	4	52	2	45	2	44	2	38	0	41	0	63	0	67	0	67
	2nd most	5	32	3	14	2	21	4	40	4	37	0	33	1	30	2	21	2	18	2	18
CT (cervical-abdominal)																					
Post-esophagectomy	Most	3	35	2	51	2	66	2	71	2	65	1	51	1	52	0	62	0	69	0	68
	2nd most	2	34	3	26	3	13	1	13	1	21	0	36	0	42	1	35	1	30	1	31
Post-dCRT	Most	4 or more	55	4 or more	38	2	62	2	75	2	68	1	49	1	45	0	64	0	68	0	67
	2nd most	3	19	2	37	3	16	1	8	1	16	0	36	0	44	1	29	1	29	1	30
Upper GI endoscopy																					
Post-esophagectomy	Most	1	74	1	88	1	86	1	87	1	90	1	69	1	66	0	55	0	58	0	56
	2nd most	2	14	0	6	0	8	0 or 2	6	2	6	0	31	0	34	1	45	1	42	1	44
Post-dCRT	Most	4 or more	53	2	38	2	55	2	62	2	56	1	58	1	55	0	59	0	63	0	60
	2nd most	2	31	4	34	1	23	1	34	1	40	0	30	0	37	1	34	1	32	1	34
Screening of H&N cancers																					
Post-esophagectomy	Most	1 or more	51	1 or more	55	1 or more	48	1 or more	52	1 or more	53	0	57	0	62	0	79	0	81	0	81
	2nd most	0	49	0	40	0	47	0	43	0	42	1	43	1	38	1	21	1	19	1	19
Post-dCRT	Most	0	51	1 or more	59	1 or more	51	1 or 2	56	1 or 2	53	0	59	0	66	0	82	0	84	0	82
	2nd most	1 or more	32	0	41	0	49	0	44	0	47	1 or 2	41	1 or 2	34	1 or 2	18	1 or 2	16	1 or 2	18

The most and the 2nd most popular frequencies of each modality for each year are shown

dCRT definitive chemoradiotherapy, *CT* computed tomography, *GI* gastrointestinal, *H&N* head and neck

[a] Tumor marker SCC-Ag is also included in the follow-up schedule by most of the hospitals

dCRT, based on the present data concerning the modalities incorporated by most of the participating hospitals and the most and the 2nd most popular frequencies of each modality for each year (Table 1). The appropriateness of this popular follow-up protocol should be verified in the future by comparing various aspects including the detection rate of recurrences and the overall survivals after treatments of recurrences between this protocol and less or more intensive ones. In addition, cost-effectiveness of each should also be considered [29]. Moreover, the patient's desire should also be taken into consideration, because Blom et al. [30] showed that two-thirds of the patients who underwent potentially curative esophagectomy for esophageal cancers preferred follow-up with routine imaging, even if screening would not provide a survival benefit.

The present study is associated with some limitations. (1) The data were only collected from 77 hospitals in Japan, which suggests the possibility that it does not represent the true status of follow-up protocols in Japan, although all of the surveyed hospitals were certified by the JES as training hospitals for a certified esophageal surgeon. (2) It is unknown whether a protocol shown here will reflect a truly favorable outcome for patients with esophageal cancer after esophagectomy or dCRT. Finally, (3) we did not consider the financial implications of costly investigations.

In conclusion, we tried to clarify the nation-wide trends in the follow-up protocol after curative esophagectomy and dCRT and attempted to propose a consensus protocol (Table 1). The suitability and efficacy of the protocol shown in the present study are not known with respect to cases of recurrent esophageal cancer. However, in spite of the above-mentioned limitations, we believe that the results of this nation-wide survey and a proposed protocol will contribute to the accumulation of larger-scale clinical data based on a fixed schedule with a consensus and to obtain evidence for making a more efficient and rational follow-up protocol to diagnose and treat recurrent esophageal cancers after curative esophagectomy and dCRT. In the future, the performance of meta-analyses using the findings of many reports on the outcome of a follow-up after a curative esophagectomy and dCRT will be necessary.

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Compliance with ethical standards

Ethical Statement This article does not contain any studies with human or animal subjects performed by any author(s).

Conflict of interest The authors declare that they have no conflict of interest.

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特集2　肝がん治療戦略のUp to Date

肝癌診療ガイドライン第3版：改訂の実際と問題点

長谷川　潔[*1,2]　國土典宏[*1,2]

The 3rd Version of Clinical Practice Guidelines for Hepatocellular Carcinoma : Revision Procedures and Current Problems : Hasegawa K[*1,2] and Kokudo N[*1,2] ([*1] Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, [*2] Group formed to revise the 3rd version Guidelines for Evidence-Based Clinical Practice for the Treatment of Liver Cancer)

The 3rd version of "Clinical Practice Guidelines for Hepatocellular Carcinoma" was revised using the methodology of the Evidence-based Medicine as had been done in the first and second editions. At first,total 57 Clinical Questions(CQs) were set, for which search formulae to pick up scientific articles were constructed. Using the formulae, in conjunction with each CQ, total 1,648 articles were systematically picked up from the PubMed and MEDLINE databases between July 2007 and December 2011. For each selected article, a structured abstract was written. By the second selection, 591 articles were adopted to be used for the revision of the Guideline. The text including recommendation for each CQ and scientific statement was written based on the structured abstracts of the finally selected article, and recommendation grade was finally decided. To secure objectivity and reproducibility, the revision work was done with attaching great importance to evidence.

Key words : Evidence based medicine, Clinical question, Treatment algorithm

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はじめに

「科学的根拠に基づく肝癌診療ガイドライン」は初版[1]が2005年2月に刊行されたが，これは厚生労働省科学研究費（班長：幕内雅敏・現日本赤十字社医療センター院長）のサポートを受け，いわゆる班研究の形で作成された．第2版以降は日本肝臓学会の事業の1つとして引き継がれ，2009年11月に第2版が刊行[2]（改訂委員会委員長：幕内）された．本ガイドラインは初版以来，一貫していわゆるEvidence-based Medicine（EBM）の手法で策定されてきたが，エビデンスが年代とともに変わっていくことを考慮し，EBMによるガイドラインは4～5年に1度の改訂が望ましいとされている．そこで，第3版の改訂は第2版発刊から約2年後の2011年9月から開始され，約2年の改訂作業ののち，2013年10月に第3版発刊[3]となった．本稿では改訂内容の詳細は他稿に譲り，改訂作業の実際とその過程で生じた問題点や今後の課題につき説明する．

1 「科学的根拠に基づく肝癌診療ガイドライン」第3版改訂の実際

本ガイドライン第3版改訂委員会は18人の委員，15人の専門委員，3人の特別委員から構成さ

*1 東京大学大学院医学系研究科肝胆膵外科
*2 肝癌診療ガイドライン第3版改訂委員会

れたが（委員長：國土典宏），作業が膨大なため，適宜実務協力者17名にも加わっていただき，最終的に総勢55名となった．

第3版改訂ではおおまかにいって以下の3つのステップを踏んでいる．まず，1）Clinical Question（CQ）の見直し・設定から作業を始めた．このCQは肝癌診療上の重要な問題点について，基本的にYes or Noで答えられる疑問文として提示される．2）次にそれぞれのCQに対応するエビデンスを論文の中から抽出し，scientific statementとしてまとめ，CQに対する診断や治療面での対応に関する「推奨」を作成する．3）さらにエビデンスのレベルを判定し，それに基づいて「推奨」や「根拠」の強さを決め，グレードとして示す．これらの過程はいわゆるEBMの基本手法で，初版以来，本ガイドラインでは一貫して遵守してきた．「専門家の個人的な意見」はできるだけ排除し，あくまでエビデンスに基づいたコンセンサスを求めるよう，留意した．

CQの設定について，初版では論文を一次選択し，そこから絞り込んでいく過程の中でresearch question（第2版以降はCQに名称変更）が決められたのに対し，第2版では先にCQをある程度確定させてから，論文検索に取りかかった．時間がたてば，新たなエビデンスにより，CQの対象など設定を修正すべきであり，各CQの意義そのものが変化しても不思議ではない．先にCQの内容を十分に検討しておくほうが効率良いと思われるため，第3版もこの第2版のやり方にならった．第2版のCQ 51個のうち13個が統廃合で除かれ，残り38個のうち，17個が修正なしで採用，21個が何らかの修正の後に採用．これらに新設CQ19個が加わって，第3版のCQは合計57個となった．

このCQをもとに検索式を作成し，論文データベースから各CQに関する論文を系統的に一次選択した．論文データベースとして，初版はMEDLINEと医中誌，第2版はPubMed，第3版ではPubMedとMEDLINEを採用したが，初版以来，基本的に英文論文を優先して拾い上げる方針である．この検索式作成には専門知識が必要で，図書館司書の方にご協力をお願いした．優れた検索式（必要かつ十分な論文を拾い上げられる）を設定するにはCQが論理的かつ具体的であることが求められるので，その点を最初から意識して，CQを設定することが肝要である．初版では1982年から2002年の長い期間を検索対象としたため，45,974本の論文の中から7,118本もの論文が一次選択された．第2版では2002年10月から2007年6月と対象期間が短くなったゆえ，3,095本から576本が一時選択された．第3版では2007年7月から2011年12月が対象期間となり，第2版と同程度だったが，第3版の新規CQが19個と多く（第2版では7個），新規CQについては1982年にさかのぼって検索が行われたため，6,750本の中から1,648本が一次選択された．第2版と同様，対象期間のあと（すなわち第3版では2012年1月以降）に発表された論文はいかに重要であっても，付記にとどめることにした．ただし，昨今のインターネット環境の進歩や電子ジャーナルの普及を考慮し，第3版では期間内にe-pub ahead printingとして公表された論文は検索対象に加えた．

次に，一次選択された論文1,648本につき，それぞれ構造化抄録を作成する作業に入った．構造化抄録は各論文につき，目的・対象と研究方法・結果・結論に加え，デザインの種類，研究期間・施設や対象症例数，評価項目や統計手法などの情報も論文内容から拾い上げ，系統的に記載したもので，これにより論文のエビデンスの内容やレベルが一目で把握可能となり，ガイドライン構築に必要な論文がより客観的により容易に取捨選択できるようになる．1,648本の一時選択論文は二次選択で709本に絞られ，最終的には591本が採択となった．591本のうち，初版・第2版からの繰り越しが241本，残り350本が新規採択であった．

これらの作業の後，各CQに対する推奨文案が各担当委員によって作成され，会議において吟味・修正の後，確定された．さらに推奨の根拠となるエビデンスの強さ（多くの場合，研究デザインや症例数が根拠となる）に応じて，推奨のグレードが決定された．2013年4月にガイドライン全体の素案が完成され，同年5月，日本肝臓学会のホームページ上で公開された．第49回日本肝臓

学会総会（会長：工藤正俊近畿大学消化器内科教授）の特別企画として，2013年6月7日に公聴会が開催され，同時にパブリックコメントが公募された．寄せられた意見は委員により検討され，一部は修正に反映された．日本肝臓学会の企画広報委員会・理事会の承認を得て，2回の校正の後，2013年10月に発刊の運びとなった．今回の改訂では合計8回の委員会が開かれ，ほぼ2年を費やす膨大な労力を要したが，今まで同様，検索式や構造化抄録はすべて公開し，改訂作業の客観性と再現性の担保としており，これら全作業工程は時間はかかっても必要な手順だったと考えている．

2 「科学的根拠に基づく肝癌診療ガイドライン第3版」の主たる変更点

まず，第3版では章立てが大きく変更となった(表)．最近の化学療法と放射線治療の目覚ましい進歩をふまえ，第2版では両者あわせて一つの章だったのをそれぞれ独立した章として扱った．さらに第2版まではCQは基本的に初発肝がんを想定した設定だったが，再発への対応が臨床上重要な点を考慮し，第3版では「治療後のサーベイランス，再発予防，再発治療」という新章を設けた．章の順序を一部変更し，最終的に全部で8章という構成（初版・第2版は全6章）となった．

表　第3版の構成

サーベイランス・診断アルゴリズム
治療アルゴリズム
第1章：予防
第2章：診断およびサーベイランス
第3章：手術
第4章：穿刺局所療法
第5章：肝動脈化学塞栓療法
第6章：化学療法
第7章：放射線治療
第8章：治療後のサーベイランス，再発予防，再発治療

サーベイランス・診断アルゴリズム第3版の変更点

肝癌サーベイランス・診断アルゴリズム[3](図1)では，初版以来，スクリーニングの第1選択は超音波検査，次に必要であればdynamic CT/MRI，という位置づけであった．今回も超音波検査の簡便さ，低侵襲性，低コスト，診断能の高さなどが重視され，超音波検査で拾い上げ，dynamic CT/MRIで確定診断を得るという基本構造は踏襲された．また，「典型的肝細胞癌像」を「早期造影効果」と「後期washout」の併存として定義し，画像所見だけで確定診断に至るという点も同じである．ただし，最近の画像検査の著しい進歩を鑑み，以下の点で修正が加えられた．

1）前版までは「典型的肝細胞癌像」の有無でアルゴリズムを構築したが，「典型的肝細胞癌像」の判断根拠となる「早期造影効果」と「後期washout」の2つの所見を分けて，アルゴリズムに取り入れることになった．

2）両者が同時に「あり」なら，以前と同様，肝細胞癌の確定診断となるが，両者がともに陽性とならない場合のOption検査の適応基準が今回変更となった．前版までは一律腫瘍径2cm超でOption検査を行うことになっていたが，第3版では「早期造影効果あり」で「後期washoutなし」の場合，腫瘍径1cm超，「早期造影効果なし」では腫瘍径1.5cm超，となった．つまり，大きさの基準が引き下げられ，早期造影効果の有無で基準に差がつけられたことになる．この修正に強いエビデンスがあるわけではないが，2cm以下の肝がんが日常的に確定診断をつけられて，治療されている現状が考慮された．

3）Option検査の中にGd-EOB-DPTA造影MRIが追加された．

3 治療アルゴリズム第3版について

肝癌治療アルゴリズム[3]（図2）は「科学的根拠に基づく肝癌診療ガイドライン」のエッセンスの集約であり，臨床現場でもっとも利用されている部分である．エビデンスに基づいた治療法が肝障害度，腫瘍数，腫瘍径の3つの因子により，簡便に選択できることを目指し，初版以来，シンプ

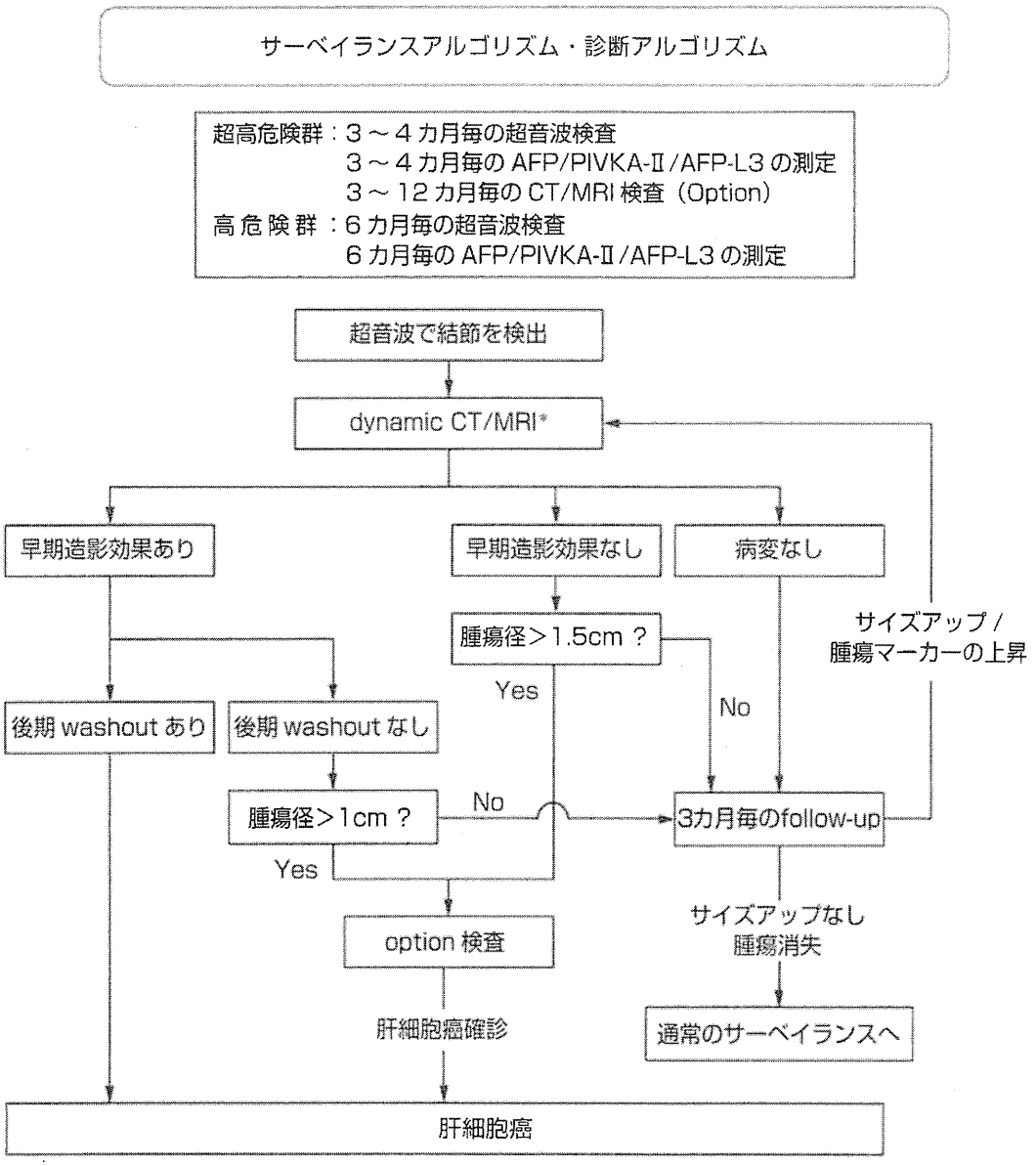

図1　科学的根拠に基づく肝細胞癌サーベイランス・診断アルゴリズム（文献3より引用）

ルで使いやすいという点を最重要視し，構築された．第3版もその基本方針は踏襲されたが，以下の3点で改訂が加えられた．

1）肝切除と焼灼療法（第2版では局所療法と記載）に優先順位を明確にした．すなわち，肝障害度AまたはB，腫瘍数単発では肝切除が第1選択に挙げられ，さらに腫瘍径3cm以内なら，焼灼療法が第2選択と明記された．その根拠となったのは，日本肝癌研究会の全国調査データを用いた解析結果である[4,5]．これらはコホート研究であり，背景因子の違いによる影響を完全には排除しえないため，本来ランダム化比較試験（以下RCT）の結果に先んずるものではない．しかし，検索対象内で両治療法を比較した3本のRCTのいずれも何らかの問題があり，アルゴリズムに反映するべきエビデンスとはいいがたいと判断された．肝障害度AまたはB，腫瘍数2－3個，腫瘍径3cm以内の場合は同じ日本肝癌研究会の全国調査データを用いた結果を根拠に肝切除と焼灼療法が並列記載（優先順位なし）となった[4,5]．

2）ソラフェニブに関するエビデンス[6]を考慮し，第3版からアルゴリズムにも取り入れることになった．もともと切除，局所療法，塞栓療法など既存の有効性が証明された治療が適応外で，か

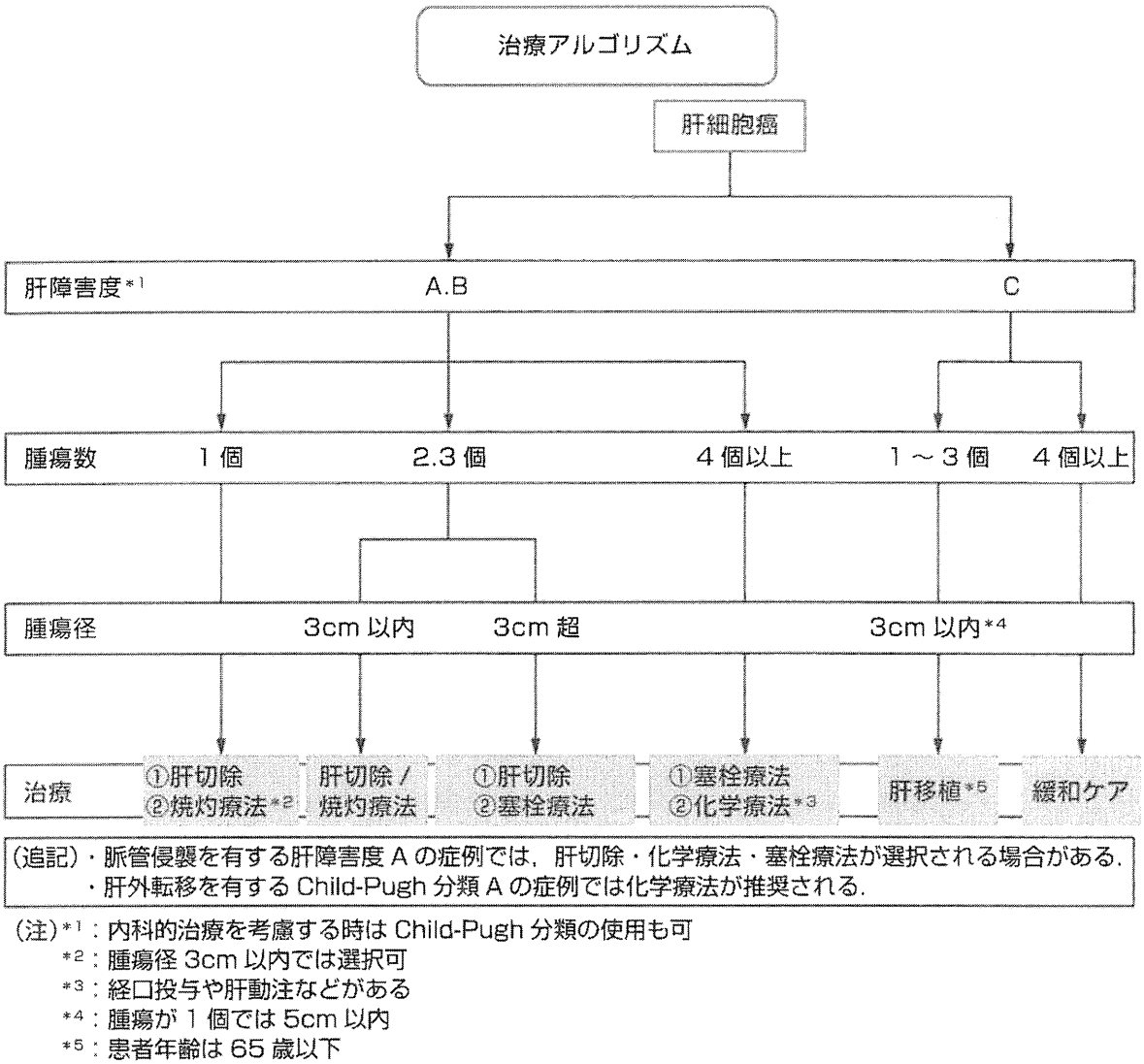

図2　科学的根拠に基づく肝細胞癌治療アルゴリズム（文献3より引用）

つ比較的肝機能がよい症例が対象なので，肝障害度AまたはB，腫瘍径にかかわらず，腫瘍数4個以上の条件で塞栓療法の次に位置づけることになった．ここは第2版まで肝動注療法が占めていた位置である．現時点で肝動注のエビデンスが十分とはいえない状況に変わりはないが，今後の可能性を残すということでソラフェニブと合わせ，化学療法という記載でひとまとめとし，「経口投与と肝動注などがある」という注釈をつけた．他の薬剤が今後登場する可能性を考慮し，ソラフェニブという固有名詞はあえてアルゴリズムの中には入れなかった．

3）肝機能の評価として，初版以来，肝障害度が採用されているが，これにはIndocyanine green（ICG）を用いた検査が必須である[7]．しかし，局所療法や塞栓療法など切除以外の治療が行われる場合，必ずしもICG検査が行われていない現状をふまえ，内科的治療を考慮するとき，という条件付きでChild-Pugh分類の使用も可能となった．

4 第3版改訂作業中に認識された問題点・今後の課題

今回改訂中に議論された主な問題点は，

1）ガイドラインに利用できるエビデンスが少

ない，あるいはエビデンスの乏しい領域で日常臨床との乖離をどう埋めるべきか？
2) 日本にそのまま取り入れがたい海外のエビデンスをどう扱うべきか？
3) メタアナリシスの取り扱い方．
4) 検索対象期間後の新エビデンスをどう扱うか？

などが挙げられる．

1) については，全51のCQに対し，グレードAの強い推奨が13しかなかった点に反映されているといえるが，根本的には我々臨床家が必要なエビデンスを作っていくしかないと思われる．今回の作業で次回改訂に向けて求められるエビデンスが浮き彫りになったが，たとえば肝障害度とChild-Pugh分類の妥当性の比較検討，肝動注化学療法の有効性，脈管侵襲や肝外転移を伴う進行肝がんに対する治療選択，などは検討を急ぐべき重要性の高いトピックと思われた．

2) や3) については個々の論文を読み込んで，検討するよりなかった．とくにメタアナリシスは論文数が増えているが，non-RCTとRCTの結果を十分な吟味なくして，統合解析したものが多く，それゆえ結果をエビデンスレベルIaとはとうてい扱いえないものばかりであった．

4) については議論の結果，前述のようにe-pub ahead printingを含めることで対応した．

次に今後の課題として，

a. ガイドラインの推奨の妥当性をどう評価するか？
b. アウトカムの向上にいかにつなげていくか？
c. 予算の確保と委員の負担の軽減
d. 医療経済の視点をどうガイドライン構築に取り入れるべきか？

などが考えられる．

aについて，ガイドラインの推奨の妥当性はアウトカム（治療成績すなわち長期生存）の改善にいかに寄与したかで判断されるべきと考えれば，治療効果をいかに客観的に評価するかという問題に行きつく．この点でaはbとほぼ同じ課題と思われるが，現実的にはアプローチが難しい．本来，生存率による評価が理解しやすいのだが，評価できるまでに時間がかかるのと，関与する因子が多すぎて，1つの治療の効果だけを取り出すことが困難という問題点がある．これらを克服するために，最近，Quality indicatorというプロセス指標による評価法が使われるようになったが，カルテからデータを拾い上げるのに手間と時間がかかりすぎる運用上の問題がある．肝癌領域ではがん登録が比較的機能しているので，ガイドライン改訂委員会の守備範囲ではないが，現在，日本肝癌研究会の追跡調査委員会に働きかけ，調査項目を工夫することで登録データからQuality indicatorを実測できるように調整している．肝がん登録はNational Clinical Databaseへの移行作業中で，調査項目の調整も同時進行で行っているが，うまくいけば，数年後にはaとbの課題について一定の成果が得られると期待される．

cについて，初版では科研費という形で公的サポートが得られたが，第2版・第3版では学会による実費（交通費他）のカバーのみであり，事実上委員のボランティアに頼った格好である．他領域のガイドラインも大なり小なり同様の問題を抱えていると予想されるが，幸い肝癌では学会のご配慮で図書館司書の方の支援が得られ，これで委員の負担は大きく軽減された．

dについては重要なポイントであるが，確立された方法がなく，人的資源も乏しいため，今回はごく限られた領域について，医療経済学的な見解を記載しただけにとどまった．今後の課題である．

また，第3版発行から本稿投稿時まで1年3カ月が経過したが，その間，外部評価と英訳作業を進めてきた．英訳版は最近刊行され[8]，外部評価については近日中にその結果を公表できる見込みである．

おわりに

「科学的根拠に基づく肝癌診療ガイドライン」は初版以来，EBMの手法にのっとり，客観性の高いエビデンスを抽出し，根拠のない「思い込み」を排除するように構築されてきた．第3版もその基本方針に大きな変更なく，最新のエビデンスを盛り込むように留意した改訂となった．

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X 原発性肝癌取扱い規約・科学的根拠に基づく肝癌診療ガイドライン

取扱い規約(第5版改訂版)とTNM分類(第7版)

The general rules for the clinical and pathological study of primary liver cancer (5th version) and the TNM classification (7th version)

長谷川 潔　　國土典宏

Key words：日本肝癌研究会，脈管侵襲，リンパ節転移，破裂

はじめに

本来，癌の取扱い規約とは共通の決まりに従って，当該癌腫の症例経験を蓄積・整理し，データの質を担保することが第一の目的であり，その得られたデータから診断や治療のあり方を検討し，最終的には治療成績向上につなげることを目指している．肝癌の場合，その決まりに従って，肝機能や腫瘍の条件(大きさや数，存在部位など)，治療法，病理所見といった臨床的に重要な情報を漏れなく，記録することになる．したがって，規約と日常臨床に大きな乖離があってはならない．一方で臨床データは自国内の治療成績の向上にのみ寄与するのではなく，全世界的に活用されるべきとも考えられ，とすれば，国際的に共通のルールで整理される方が望ましいといえる．しかし，日本と海外の肝癌診療に種々の点で大きな違いが存在し，両者を同時に満足するのは容易ではない．本稿では日本肝癌研究会による原発性肝癌取扱い規約[1]とInternational Union against Cancer/American Joint Committee on Cancer(UICC/AJCC)によるTNM分類の相違について概略を紹介し，肝細胞癌におけるそれぞれの問題点を論じた．なお，UICC/AJCCのTNM分類と記載したが，正確にいうと，AJCCの'Cancer Staging Manual'[2]ではTNM分類に加え，肝の解剖，リンパ節の部位や遠隔転移の定義，背景肝の線維化の評価，TNM分類の根拠など，より詳細な説明がなされ，UICCの'Classification of Malignant Tumours'[3]にはTNM分類だけ抜粋され，掲載されている．ここではあわせて'UICC/AJCCのTNM分類'と称することとする．

1 現在の原発性肝癌取扱い規約とUICC/AJCCのTNM分類の相違

1987年，UICC/AJCCによるTNM分類第4版に肝癌の分類が初めて登場したが，これは日本の原発性肝癌取扱い規約第2版そのものであった．これには当時，肝癌の診療における我が国の国際的な地位の高さが少なからず影響したと思われる．その後，両者は独自に改訂が行われ，違いがみられるようになった．現在，原発性肝癌取扱い規約は第5版補訂版[1]，UICC/AJCCのTNM分類は第7版[2,3]が用いられている．

1) T因子の相違

T因子については，原発性肝癌取扱い規約(図1)もUICC/AJCCのTNM分類(表1)も'腫瘍径'，'腫瘍数(単発or多発)'，'脈管侵襲の有無'の3項目の組み合わせで分類する基本的考え方は同じだが，3項目それぞれの取扱いには

Kiyoshi Hasegawa, Norihiro Kokudo: Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo　東京大学大学院医学系研究科 臓器病態外科学 肝胆膵外科

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Special Report

Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines)

Norihiro Kokudo, Kiyoshi Hasegawa, Masaaki Akahane, Hiroshi Igaki, Namiki Izumi, Takafumi Ichida, Shinji Uemoto, Shuichi Kaneko, Seiji Kawasaki, Yonson Ku, Masatoshi Kudo, Shoji Kubo, Tadatoshi Takayama, Ryosuke Tateishi, Takashi Fukuda, Osamu Matsui, Yutaka Matsuyama, Takamichi Murakami, Shigeki Arii, Masatoshi Okazaki and Masatoshi Makuuchi

The Committee for Revision of the Clinical Practice Guidelines for Hepatocellular Carcinoma, Tokyo, Japan

The 3rd version of Clinical Practice Guidelines for Hepatocellular Carcinoma was revised by the Japan Society of Hepatology, according to the methodology of evidence-based medicine, which was published in October 2013 in Japanese. Here, we briefly describe new or changed recommendations with a special reference to the two algorithms for surveillance, diagnosis, and treatment.

Key words: algorithm for surveillance and diagnosis, algorithm for treatment, clinical practice guidelines, clinical question, evidence-based medicine

INTRODUCTION

THE SECOND VERSION of Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma (2nd JSH-HCC Guidelines) conducted by the Japan Society of Hepatology (JSH) was published in 2009 in Japanese, and its English version was released in 2010.[1] Because new knowledge and information have been increasingly accumulated since the end-point of the published work search in June 2007, the second revision was initiated in September 2011, and the new third version was published in October 2013 in Japanese.

As was the case in the first[2–4] and second[1] versions of the JSH-HCC Guidelines, the third was strictly revised by the methodology of evidence-based medicine. In the revision procedures, we set a total of 57 clinical questions (CQ), constructed retrieval styles for each CQ, and systematically searched scientific papers ($n = 6750$ in total) published between July 2007 and December 2011 in the medical databases (PubMed and Medline) by the retrieval styles. The entire published work search formula is open to the public (https://www.jsh.or.jp/English/), which has not been always the case in other HCC guidelines. After critical reading of all abstracts and sometimes whole manuscripts (when necessary) for a total of 1648 relevant publications, we finally selected a total of 596 papers, wrote recommendations for each CQ and decided the grade of the recommendations.

The full English version of the 3rd JSH Guidelines is available including the retrieval styles for all clinical questions on the JSH website (https://www.jsh.or.jp/English/). Herein, we highlight the important revision points in recommendations and algorithms in the new guidelines.

ALGORITHM FOR SURVEILLANCE AND DIAGNOSIS

THE FUNDAMENTAL STRATEGY for HCC surveillance and diagnosis is demonstrated in a revised

Correspondence: Dr Norihiro Kokudo, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: kokudo-2su@h.u-tokyo.ac.jp
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Original article

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Tumour characteristics, treatment patterns and survival of patients aged 80 years or older with colorectal cancer

K. Kotake*, M. Asano†, H. Ozawa*, H. Kobayashi‡ and K. Sugihara‡

*Department of Colorectal Surgery, Tochigi Cancer Center, Utsunomiya, Japan, †Department of Surgery, Asano Clinic, Hamamatsu, Japan and ‡Department of Surgical Oncology, Graduate School, Medical and Dental University, Tokyo, Japan

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Abstract

Aim This study aimed to clarify tumour characteristics and treatment patterns for patients with colorectal cancer aged 80 years or older and the impact of age on survival using a large-scale cancer registry database.

Method The database was used to identify 40 851 colorectal cancer patients who underwent surgery between 1995 and 2004. Patients were stratified into four age groups (< 50, 50–64, 65–79, ≥ 80 years). Demographics, tumour characteristics, treatment pattern and survival were compared between age groups. Additionally, the impact of lymph node dissection and adjuvant chemotherapy on survival was studied using the propensity score-matching method.

Results In the over 80 age group, patients were more commonly female, with right colon cancer, multiple primary cancers, history of colorectal cancer, high serum carcinoembryonic antigen values, large tumour, undifferentiated histology, and more frequent pT3/pT4 tumours. In contrast, metastatic disease, central lymph node dissection and adjuvant chemotherapy were less frequent. Overall survival and cancer-specific survival decreased with increasing age for any stage. Multivariate analysis showed age to be an independent predictor of overall survival (hazard ratio 1.45, 95% CI 1.34–1.58, $P < 0.001$). In the propensity score-matched cohort, overall survival of the patients with central node dissection and having adjuvant chemotherapy was significantly better than for those without. This difference was not statistically significant in patients aged 80 and above.

Conclusion This study showed a significant difference in tumour characteristics and treatment patterns in patients aged 80 and above. Even after adjustment for clinicopathological factors, the difference in survival persisted and age was considered a robust prognostic factor.

Keywords Octogenarian, surgery, colorectal cancer, characteristics, survival

What does this paper add to the literature?
Large-scale detailed data from a cancer registry in Japan were used to assess the prognostic factors of colorectal cancer in patients aged over 80 years. To date, few studies have investigated this subject, particularly in Asian countries where the burden of this disease is drastically increasing.

Introduction

Colorectal cancer (CRC) is the fourth most common cause of cancer death worldwide [1]. Because it predominantly occurs in the elderly, the incidence and mortality of the disease are expected to increase continuously as the population ages [1]. In Japan, among approximately 110 000 new cases of CRC were diagnosed in 2008, 70% of which were in people aged over 65 years and 40% over 75 years [2], and the CRC mortality in these age groups has markedly increased.

Various studies have shown age to be a negative predictor of prognosis [3–9]. Most of these studies suggested that poor survival of the elderly is partly due to a higher operative mortality because of physical frailty [6–8], but others have suggested that differences in biological characteristics of the disease and/or treatment patterns such as chemotherapy could affect their poor prognosis [9]. To date, however, the impact of increasing age on clinical and pathological characteristics of CRC and the long-term outcome of surgery remain poorly understood.

Correspondence to: Kenjiro Kotake, MD, PhD, Department of Colorectal Surgery, Tochigi Cancer Center, 4-9-13, Yohnan, Utsunomiya, Tochigi 320-0834, Japan.
E-mail: kkotake@tcc.pref.tochigi.lg.jp

To gain better insight into survival differences between age groups, we examined and compared tumour characteristics, treatment patterns and survival of CRC patients in the cancer registry database of the Japanese Society for Cancer of the Colon and Rectum (JSCCR). Because surgery is indisputably the most successful treatment modality for CRC, the subject of this study was limited to patients who had surgery for primary tumours.

Method

Data collection

The JSCCR has a hospital-based registration system that was begun in 1980 [10]. The member hospitals of the JSCCR located in Japan voluntarily register clinical and pathological information about patients with CRC who are treated at each hospital. The database currently contains information for 160 000 CRC patients treated between 1974 and 2004.

In this study, information on 40 851 patients with CRC who underwent surgery for primary tumours between 1995 and 2004 was extracted from the database and used for analysis. Patients of unspecified age ($n = 277$), malignancies other than adenocarcinoma or unknown tumour histology ($n = 916$), mucosal cancer ($n = 3505$), unspecified pathological stage ($n = 3974$) and unknown follow-up status ($n = 647$) were excluded from the analysis. This database did not record the type of regimen, dose or duration of administration for adjuvant chemotherapy.

In this study, the scope of lymph node dissection was described by the distance from the tumour edge (< 10 cm or ≥ 10 cm) for peri/paracolic nodes, and presence or absence of dissection for the central node at the named vascular trunk [11].

Statistical analysis

Demographic and tumour characteristics and treatment patterns were described according to the four age groups: 18–49, 50–64, 65–79 and ≥ 80 years. Summary statistics for patients were constructed using frequency and proportion for categorical variables and the mean with standard deviation for continuous variables. The difference of each variance between patients aged < 80 and ≥ 80 years was evaluated using the chi-squared test. The primary outcomes of interest in this study were overall survival (OS) and cancer-specific survival (CSS) after surgery, which was calculated in months relative to the date-of-surgery (information available from the database). Survival analysis was performed using the Kaplan–Meier method and the statistical significance of the difference between groups was tested by the log-rank test with length of follow-up being truncated at 60 months. Multivariate Cox proportional hazard analysis was performed to determine the association of demographic and tumour characteristics and treatment patterns among age groups.

In addition, the impact of lymph node dissection and adjuvant chemotherapy on OS was explored using the propensity score-matching method. We calculated propensity scores by multivariate logistic regression. Gender, treatment period, serum carcinoembryonic antigen (CEA) value, tumour site and size, histology and pathological stage were used as covariates. Using the propensity score with 1:1 nearest neighbour matching by a calliper of 0.01, we performed propensity-adjusted Cox regression analyses to determine the effect of lymph node dissection and adjuvant chemotherapy on OS. Statistical analyses were performed using SPSS Statistics version 20 (IBM Corporation, Somers, New York, USA), the SPSS plug-in PSMATCHING.3 and R version 2.12.1 (R Foundation for Statistical Computing; http://www.r-project.org). All statistical tests were two-sided and statistical significance was defined when the P-value was < 0.05.

Results

Demographics

The demographic data for 40 851 patients who underwent surgery for CRC are shown in Table 1. There were 3642 patients (8.9%) aged 18–49 years, 14 978 (36.7%) aged 50–64, 18 518 (45.3%) aged 65–79 and 3713 (9.1%) aged ≥ 80. The proportion of patients aged ≥ 80 years increased from 8.2% to 10.5% during the 10-year study period. The gender distribution differed among the age groups. In the age ≥ 80 year group, a trend for female predominance was specifically observed between 1999 and 2004.

Tumour characteristics and treatment patterns

Table 2 illustrates the tumour characteristics and treatment patterns for all CRC patients stratified by age. Patients aged between 18 and 49 presented most commonly with rectal cancer, followed by left colon and then right colon cancer, whereas right colon cancer was the most common site in those over 80 years. In the over 80 age group there were larger numbers of patients with multiple primary cancers and a history of CRC compared with other age groups. The frequency of high serum CEA levels, large tumours, undifferenti-