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Clinical Trial Note

Accelerated Fractionation versus Conventional Fractionation Radiation Therapy for Glottic Cancer of T1-2N0M0 Phase III Study: Japan Clinical Oncology Group Study (JCOG 0701)

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A randomized Phase III study was started in Japan to demonstrate the non-inferiority of survival of accelerated fractionation radiation therapy (2.4 Gy/fr) with conventional fractionation radiation therapy (2 Gy/fr) in patients with T1-2N0M0 glottic cancer. This study began in September 2007, and a total of 360 patients will be accrued from 22 institutions within 4 years. The primary endpoint is 3-year progression-free survival (PFS). The secondary endpoints are overall survival, local progression-free survival, disease-free survival, survival with preserved voice function, complete response rate, proportion of treatment completion and adverse events.

Key words: laryngeal neoplasms – radiotherapy – dose fractionation – clinical trials – phase III

INTRODUCTION

Accelerated fractionation radiation therapy has considerable benefits in terms of treatment duration and cost compared with conventional fractionation methods. In addition, some reports suggest that increased single radiation dose and shortened treatment time may improve local control (1–7). However, no multi-institutional randomized study has been conducted to show that accelerated fractionation is equivalent to conventional fractionation in terms of efficacy and safety for early glottic cancer. Various types of fractionation methods are performed in clinical practice, and according to the guidelines of the Head and Neck Cancer Disease Site Group in Canada, an optimal fractionation protocol has not yet been established (8). We therefore designed a study, which investigates whether accelerated fractionation radiotherapy is suitable for T1-2N0M0 glottic cancer in terms of survival, feasibility, voice function and safety.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in August 2007 and the study was activated in September 2007. This trial was registered at the UMIN Clinical Trials Registry as UMIN000000819 [http://www.umin.ac.jp/ctr/index.htm].

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PROTOCOL DIGEST OF THE JCOG 0701

Purpose

The aim of this study is to demonstrate the non-inferiority of the efficacy of accelerated fractionation radiation therapy (2.4 Gy/fr) with conventional fractionation radiation therapy (2 Gy/fr) in patients with T1-2N0M0 (UICC/TNM, 6th edition) glottic squamous cell carcinoma.

Study Setting

A multi-institutional randomized Phase III study.

Resources

Grants-in-Aid for Cancer Research (17-17, 16-12, 17S-5) from the Ministry of Health, Labour and Welfare of Japan.

Endpoints

The primary endpoint is the 3-year progression-free survival (PFS) proportion in all eligible patients. PFS is defined as days from randomization to first evidence of local progression, distant metastasis or death from any cause. In patients alive without events, PFS will be censored at the last visit. The secondary endpoints are overall survival, local progression-free survival, disease-free survival, survival with preserved voice function, complete response rate, proportion of treatment completion and adverse events.

Overall survival is defined as days from randomization to death from any cause. Local progression-free survival consists of time free from local disease progression or death from any cause, while disease-free survival is defined as duration free of local progression, distant metastasis, secondary cancer or death from any cause. Survival with preserved voice function is defined as days from randomization to first evidence of death from any cause or appearance of voice changes of Grade 3 or more as diagnosed by the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). The proportion of treatment completion denotes the percentage of patients whose treatment is completed within the recommended length of time: 51 days for T1 and 53 days for T2 in the conventional radiation arm, and 39 days for T1 and 43 days for T2 in the accelerated radiation arm.

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, the patient must fulfill each of the following criteria: (i) primary tumor site lies within the vocal cords; (ii) the tumor consists of histologically proven squamous cell carcinoma; (iii) the extent of the primary tumor is evaluated as T1 or T2 without impaired cord mobility; (iv) the tumor is clinically staged as N0/M0; (v) radiation therapy can be completed within the recommended duration without interruption due to national holidays; (vi) age between 20 and 80 years; (vii) ECOG performance status of 0 or 1; (viii) no prior surgery or radiation therapy of the larynx; (ix) no prior chemotherapy for any malignancies within 5 years; (x) sufficient organ function; (xi) completed written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) active bacterial or fungous infection; (ii) simultaneous or metachronous (within 5 years) double cancers; (iii) women during pregnancy or breast-feeding; (iv) psychosis; (v) treatment with systemic steroids; (vi) history of collagen disease except for rheumatism; (vii) insulin-dependent or poorly controlled diabetes mellitus; (viii) poorly controlled hypertension; (ix) history of severe heart disease, heart failure; (x) myocardial infarction or angina pectoris within the past 6 months.

Randomization

After the confirmation of the inclusion and exclusion criteria by telephone or fax to the JCOG Data Center, the patients are randomized to either conventional radiation arm or accelerated radiation arm, by the minimization method of balancing the arms according to T factor (T1/T2 by UICC/TNM, 6th edition) and institution.

Treatment Method

In conventional radiation arm, conventional fractionation radiotherapy with 2 Gy/fr (1 fr/day and 5 fr/week) is performed 33 times for a total dose of 66 Gy in patients with T1 disease, and 35 times for a total dose of 70 Gy in patients with T2 disease. Irradiation twice daily is permitted, but the maximum number of irradiation sessions per week is limited to five. It is recommended that treatment using the conventional fractionation method is completed within 51 days for T1 disease and 53 days for T2 disease.

In accelerated radiation arm, accelerated fractionation radiotherapy with 2.4 Gy (1 fr/day and 5 fr/week) is delivered 25 times for a total dose of 60 Gy in patients with T1 disease, and 27 times for a total dose of 64.8 Gy in patients with T2 disease. Twice-daily irradiation is prohibited, as is irradiation six or more times per week. Recommended duration of accelerated fractionation radiotherapy is 39 days for T1 disease and 43 days for T2 disease.

In both study arms, the gross tumor volume (GTV) is defined as the GTV of the primary tumor. The clinical target volume (CTV) in T1 disease is the entirety of the vocal cords, while the CTV in T2 disease includes a 1-cm margin surrounding the tumor in addition to the vocal cords. The planning target volume (PTV) is defined as the CTV plus a margin of 0.5-1 cm in the craniocaudal direction and 0.5 cm in the posterioanterior direction.

Follow-up

All enrolled patients are followed-up at least every 6 weeks for the first 6 months and then every 3 months for a duration of 3 years. Laryngeal fiberscope and cervical lymph node exploration by manipulation are carried out at each visit.

Study Design and Statistical Method

This trial is designed to demonstrate that accelerated fractionation radiation therapy is not inferior to the conventional fractionation method in terms of 3-year PFS. If the non-inferiority of accelerated radiation arm is verified, the accelerated fractionation method will be the preferred treatment.

The planned sample size is 360 patients, with 180 cases per arm. We anticipate 3 years of follow-up after 4 years of accrual, ensuring at least 80% power with one-sided alpha of 5% and a non-inferiority margin of 5% for the primary endpoint. This assumes an expected 3-year PFS of 80% in patients treated with the conventional fractionation method, and 85% in those treated with the accelerated fractionation method.

Interim Analysis and Monitoring

We plan on conducting two interim analyses, considering multiplicity according to the method recommended by the Southwest Oncology Group (9). The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and stop the trial early if necessary. In-house monitoring will be performed every 6 months by the Data Center to evaluate and improve study progress and quality.

Participating Institutions (From North To South)

Sapporo Medical University, Tohoku University, Saitama Cancer Center, National Cancer Center East, National Cancer Center, Tokyo Metropolitan Komagome Hospital, Tokyo Women's Medical University, Tokyo Medical Center, Keio University, Cancer Institute Hospital, University of Tokyo, Kitasato University, Niigata Cancer Center, Yamanashi University, Shinshu University, Aichi Cancer Center, Kyoto University, Osaka University, Kinki University, Osaka Medical Center for Cancer and Cardiovascular Diseases, Hiroshima University, Kyushu University.

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Conflict of interest statement
None declared.

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Patterns of Pretreatment Diagnostic Assessment and Staging for Patients with Cervical Cancer (1999–2001): Patterns of Care Study in Japan*

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Objective: To evaluate the patterns of pretreatment diagnostic assessment in uterine cervical cancer patients treated with definitive radiotherapy in Japan.
Methods: The Japanese Patterns of Care Study working group conducted a second extramural audit survey of 68 institutions and collected specific information on 631 patients with cervical cancer. All patients were treated with radiotherapy in 1999–2001. Of these, 324 patients treated without surgery were the subjects of this study.
Results: International Federation of Gynecology and Obstetrics-prescribed diagnostic procedures were performed at moderate rates in our study cohort. The performance rates of chest X-ray, intravenous urography, cystoscopy, and proctoscopy were 74, 54, 53, and 33%, respectively. Cross sectional imaging studies were frequently performed. Pelvic CT, abdominal CT, and pelvic MRI were performed in 88, 80, and 76%, respectively. Lymphangiography (1%) and surgical evaluation (1%) were rarely done. Only one patient underwent PET scans in this survey period.
Conclusions: This study demonstrated the patterns of pretreatment diagnostic assessment in cervical cancer patients treated with definitive radiotherapy in Japan.

Key words: cervix neoplasm – radiotherapy – patterns of care – FIGO

INTRODUCTION

The pretreatment assessment of cancer extension is extremely important for prognosis estimation and treatment planning. Additionally, a well-defined initial assessment enables the comparison of cancer treatment results among institutions or different treatment methods. The International Federation of Gynecology and Obstetrics (FIGO) provides a global staging system for gynecologic cancers (1). Most clinicians use this staging system in the treatment of uterine cervical cancer. The system describes the rules for stage classification in detail, and the permitted diagnostic procedures are clearly stated. However, some of the procedures included, such as intravenous urography, and skeletal X-rays, could be considered outdated. Although tumor diameter and pelvic nodal status are not accounted for in the FIGO staging system, they are estimated to be the important prognostic factors for cervical cancer (2). In several studies, tumor diameter as assessed by MRI was a significant prognostic indicator for patients with cervical cancer (3–5). Evaluation of pelvic or para-aortic lymph node status with optional imaging studies, such as CT, MRI, and lymphangiograpy, may also be useful for predicting prognosis (6).

Several studies describe the patterns of pretreatment work-up of cervical cancer in the USA (7–9); however, there are few studies from Japan. The objective of this study

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was to review the patterns of pretreatment diagnostic assessment of cervical cancer in Japan.

MATERIALS AND METHODS

Between July 2002 and June 2004, the Japanese Patterns of Care Study group (JPCS) conducted a national survey of patients with cervical cancer treated with radiotherapy. Sixty-eight out of 640 institutions were selected for the survey with a stratified 2-staged cluster sampling method (10). Prior to random sampling, all institutions were classified into one of four groups. The criteria for stratification have been detailed elsewhere (10). In brief, the JPCS stratified Japanese institutions as follows: A1, academic institutions treating $\geq$430 patients annually; A2, <430 patients; B1, non-academic institutions treating $\geq$130 patients annually; B2, <130 patients. Academic institutions included cancer center hospitals and university hospitals. Non-academic institutions consisted of other facilities, such as national, prefectural, municipal, and private hospitals.

The JPCS surveyors performed on-site chart reviews at each participating facility using an originally developed format for cervical cancer. Data collection included patient characteristics (e.g. patient history, age, performance status, laboratory data, pathology, and stage), details of pretreatment work-up, therapeutic information (e.g. radiotherapy, chemotherapy, and surgery), and treatment outcome. Patient eligibility criteria of the survey were as follows: (i) carcinoma, (ii) treatment between January 1999 and December 2001, (iii) no distant metastases, (iv) no prior or concurrent malignancy, (v) no gross para-aortic lymph node metastases, and (vi) no previous pelvic radiotherapy. The JPCS collected clinical data on 631 patients with uterine cervical cancer who were treated with radiotherapy from 68 institutions. In this study, 324 patients treated by radiotherapy without planned surgery (definitive radiotherapy) were analysed. These included 115 patients from A1 institutions, 70 patients from A2 institutions, 104 patients from B1 institutions, and 35 patients from B2 institutions.

Statistical significance was tested using the chi-square test. Cases with 'unknown' and 'missing' values were combined in the tables because their meanings were the same in most cases: no valid data were found in the given resources (11).

RESULTS

Table 1 describes the patient characteristics in the JPCS 1999–2001 survey of cervical cancer patients treated with definitive radiotherapy. Table 2 shows the performance rates of the diagnostic procedures. Of the diagnostic procedures prescribed by FIGO, three quarters of the patients underwent a chest X-ray. Other examinations, such as intravenous urography, cystoscopy, and proctoscopy, were performed in approximately 30–50% of the patients. Table 3 shows the performance of the examinations according to stage. A substantial number of early stage (I, II) patients underwent these diagnostic tests prescribed by the FIGO system. Majority of the patients underwent both pelvic and abdominal CT. Pelvic MRI was also frequently performed. CT and MRI were performed mostly irrespective of stage. Lymphangiography (LAG) and surgical staging were rarely performed. Only one patient underwent PET examination in the survey period.

Tumor diameter was recorded in 75% (242/324). The tumor diameter evaluation rates by FIGO stage were 67% (29/43) for stage I, 83% (85/102) for stage II, 77% (94/122) for stage III, and 80% (28/35) for stage IVA ($P = 0.01$). MRI was the most common modality for evaluating tumor size (47%) followed by CT (16%). Only a small percentage of patients had a tumor size evaluation consisting of only a pelvic examination (6%). Tumor size increased significantly with increasing stage. Median tumor size was 26 mm (range: 0–45 mm) for stage I, 40 mm (range: 15–90 mm) for stage II, 46 mm (range: 15–100 mm) for stage III, and 55 mm (range: 30–100 mm) for stage IVA ($P < 0.0001$). Pelvic nodal status was recorded in 82% (266/324) of the patients surveyed. The pelvic nodal assessment rate by stage was 88% (38/43) for stage I, 86% (88/102) for stage II, 83%

Table 1. Patient and tumor characteristics of 324 patients with uterine cervical cancer treated with radiotherapy

Characteristics	No. of patients	(%)
Total no.	324	
Age (years)		
Range	26–100	
Median	71	
KPS		
$\leq$ 70	64	20
80	103	32
90	114	35
100	21	6
Unknown/missing	22	7
Histology		
Squamou cell carcinoma	300	93
Adenocarcinoma	14	4
Adenosquamous cell carcinoma	4	1
Other	2	1
Unknown/missing	4	1
FIGO stage		
I	43	13
II	102	31
III	122	38
IVA	35	11
Unknown/missing	22	7

KPS, Karnofsky performance status; FIGO, International Federation of Gynecology and Obstetrics.

Table 2. Pretreatment diagnostic procedures performed

Procedure	No. of patients	(%)
Chest X-ray		
Yes	241	74
No	7	2
Unknown/missing	76	24
Intravenous urography		
Yes	176	54
No	68	21
Unknown/missing	80	25
Cystoscopy		
Yes	171	53
No	60	19
Unknown/missing	93	28
Proctoscopy		
Yes	108	33
No	114	35
Unknown/missing	102	32
Pelvic CT		
Yes	286	88
No	8	3
Unknown/missing	30	9
Abdominal CT		
Yes	258	80
No	14	4
Unknown/missing	52	16
Pelvic MRI		
Yes	246	76
No	39	12
Unknown/missing	39	12
Lymphangiography		
Yes	3	1
No	241	74
Unknown/missing	80	25
PET		
Yes	1	-
No	254	79
Unknown/missing	69	21
Surgical staging		
Yes	3	1
No	257	79
Unknown/missing	64	20

PET, positron emission tomography.

(101/122) for stage III, and 94% (33/35) for stage IVA ($P = 0.12$). CT was most frequently used for the assessment of nodal status (72%). PET and surgical examination were never utilized for this purpose. Positive nodal status significantly correlated with FIGO stage: 2% for stage I, 6% for stage II, 16% for stage III, and 49% for stage IVA ($P = 0.0001$).

DISCUSSION

This study demonstrated the patterns of pretreatment diagnostic assessment for cervical cancer patients who underwent definitive radiation therapy between 1999 and 2001 in Japan. Several of the cases reviewed in this survey had unknown or missing data; and this was a theoretical weaknesses of our audit. Inclusion of cases with incomplete information in the ratio calculations, however, reduced the potential for overestimation of performance rates of the tests.

FIGO permitted procedures were performed more frequently than expected in the patients surveyed. The use of FIGO permitted examinations (e.g. intravenous urography, cystoscopy, and proctoscopy) is gradually decreasing in the USA (7–9). In a 2000–02 US study on the pretreatment evaluation of patients with stage IIB or less disease, the rates for performing intravenous urography, cystoscopy, and proctoscopy were 1, 16, and 17%, respectively (9). In contrast, the present study demonstrated that these exams were performed frequently even for early stage cases in Japan. Schmitz et al. (12) proposed that since the likelihood of upstaging using these examinations was very low in clinical stage IB patients, these exams could be omitted in those with stage IB disease. Now, the National Comprehensive Cancer Network (NCCN) guideline states that cystoscopy and proctoscopy are optional exams for the pretreatment assessment of cervical cancer patients with a disease stage of IB2 or higher (http://www.nccn.org/professionals/physician_gls/PDF/cervical.pdf).

This study demonstrated that CT and MRI were routinely utilized during the surveyed period in Japan. Tumor size and pelvic nodal status are considered to be extremely important prognostic factors for cervical cancer (2). Several studies showed the accuracy of MRI for measuring tumor diameter for uterine cervical cancer (13,14). In the 1990s, several researchers reported that tumor diameter, as assessed by MRI, significantly affected the outcome of cervical cancer patients treated with definitive radiotherapy (3–5). The radiological evaluation of lymph node metastases is also valuable in cervical cancer patients, with both CT and MRI having high predictive values (6). MR imaging had an accuracy of 93%, with 62.2% sensitivity and 97.9% specificity when a minimum axial diameter of 1.0 cm was adopted as a size criterion for detection of pelvic nodal metastases (15). The results of our study reflect the penetration of these findings into the clinical practice in Japan. Unfortunately, we were unable to precisely measure the performance rates of the assessments of tumor diameter and lymph node status due to a flaw in the survey format. Namely, we were unable to distinguish whether the assessments were performed by

Table 3. Pretreatment diagnostic procedures performed according to the FIGO stage

Procedure	Stage				Missing/unknown
	I	II	III	IVA	
Intravenous urography	17/43 (40%)	53/102 (52%)	74/122 (61%)	26/35 (70%)	6/22
Cystoscopy	18/43 (42%)	58/102 (57%)	64/122 (52%)	25/35 (71%)	6/22
Proctoscopy	12/43 (28%)	32/102 (31%)	43/122 (35%)	17/35 (49%)	4/22
Pelvic CT	40/43 (93%)	89/102 (87%)	112/122 (92%)	34/35 (97%)	11/22
Abdominal CT	35/43 (81%)	83/102 (81%)	103/122 (84%)	29/35 (83%)	8/22
Pelvic MRI	31/43 (72%)	84/102 (82%)	88/122 (72%)	27/35 (77%)	16/22

the treating physicians or were performed anew by the visiting surveyors at the time of the analysis. Despite this limitation, we were able to roughly approximate the tumor diameter and the lymph node status in each stage. In the next JPCS presently being conducted, the format has been revised to clarify the aforementioned points. Our data will aid in comparing outcome between Japan and other countries. Abdominal CT has diagnostic value in detecting extrapelvic metastases (i.e. liver and para-aortic node) and the presence of hydronephrosis or a non-functioning kidney. Despite the potential usefulness of CT and MRI, these cross-sectional imaging studies are listed as optional examinations in the FIGO system (1). FIGO also acknowledges the usefulness of these exams. However, FIGO does not accept them for staging purposes, primarily because these instruments are not generally available in developing countries. The FIGO system clearly states that findings from these exams should not be the basis for staging (1). Improper application of these exams could lead to staging migration (2). However, we believe that these cross-sectional imaging studies should be applied universally not to determine FIGO stage but to assess important prognostic factors, namely tumor diameter and nodal status.

Several randomized clinical trials (RCTs) performed in the USA demonstrated the therapeutic value of concurrent chemoradiotherapy (http://www.cancer.gov/newscenter/cervicalcancer). Most of these trials required extensive evaluation of para-aortic lymph nodes by surgical exploration or LAG. This limits the translatability of the recommendations from these trials to the Japanese clinical practice. LAG and surgical staging were rarely performed for patients in our survey. Although Eifel reported that lymph nodal status was assessed by LAG in 13.6%, and surgical evaluation in 12.2% in the US PCS (1996–99), other studies revealed that, the performance of LAG has been decreasing recently (7–9). A similar problem exists in the evaluation of tumor diameter. In the US RCTs, tumor diameter was determined by physical examination. However, tumor size assessment by physical examination is highly subjective. Thus an objective method such as CT or MRI is preferable particularly when patients are being stratified in a clinical trial. This would facilitate the translation of evidence to clinical practice.

PET was rarely performed during the study period in Japan despite being shown to be useful in the late 1990s (16). Its application is expected to increase in the future, because the Japanese health insurance plan has covered it since 2004.

In summary, the JPCS describes the general patterns of pretreatment diagnostic assessment in cervical cancer patients treated with definitive radiotherapy during 1999–2001 in Japan. Patterns of pretreatment work-up should be continuously monitored in order to avoid staging migration, to properly treat individual patients, and to fairly compare treatment methods.

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Conflict of interest statement

None declared.

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X. 臨床腫瘍学の教育

NPO法人日本臨床腫瘍学会による教育

Education of Medical Oncology by Japan Society of Medical Oncology

大江裕一郎

Key words：がん薬物療法専門医，がん治療認定医，日本臨床腫瘍学会

はじめに

1993年に発足した日本臨床腫瘍研究会を前身に日本臨床腫瘍学会(Japan Society of Medical Oncology: JSMO)は，第15回日本臨床腫瘍研究会総会で学会として再出発することが承認され，2002年3月に学会(任意団体)として発足した[1]．

1993年より開催された15回の研究会では，欧米に比較して遅れていた我が国の臨床試験の方法論および基盤整備，臨床腫瘍医の育成および教育研修，トランスレーショナルリサーチなどが取り上げられ，時には行政の担当者も交え激しくかつ建設的な討論が行われてきた．このような活動を通じて，日本臨床腫瘍研究会は少なからず我が国の臨床腫瘍学の進歩に貢献してきた．その間，新GCPが施行されたこともあり，我が国の臨床研究，特に治験の質は大きく向上し，当初の目的はある程度達成された．また，日本臨床腫瘍研究会発足当時は皆無であった治験コーディネータも現在では臨床現場で活躍しており，臨床試験の質の向上に貢献している．このように，いまだ不十分ではあるものの治験を実施する環境は急速に整備されてきている．一方，医師主導治験が開始されているが，医師の実施する臨床試験は一部の多施設共同試験グループを除いて体制も不十分で満足のいく状態ではなく，これらの基盤整備の推進が望まれる．

一般臨床においても，がんの薬物療法を専門とする医師は極めて少なく，我が国で抗がん剤治療が適切に行われているとは言い難い状況である．このような状況を解決するためには，臨床腫瘍医(medical oncologist)の育成および底辺の拡大が極めて重要であり，これは社会の要望であるとともに日本臨床腫瘍学会が取り組むべき最も大きな課題である．臨床腫瘍医とは，がんの基礎研究を理解し，創出された薬物の臨床研究を科学的，倫理的に実施する臨床研究医であるとともに，がんの薬物療法を安全に行うのみならず，緩和ケアを含め，がん患者を総合的に診療できる臨床医である必要がある．このような医師を育成することが，我が国の臨床腫瘍学発展のためには不可欠である．

1. ‘臨床腫瘍専門医’から‘がん薬物療法専門医’へ

日本臨床腫瘍学会設立目的の一つである臨床腫瘍医の教育，育成のために，2002年より臨床腫瘍専門医制度規則・細則の制定，研修カリキュラムの策定，教育セミナー開催，暫定指導医・認定研修施設の認定，学会の法人化など専門医認定の準備が順次進められてきた(表1)．これらの作業は，粛々と進められてきたが，決し

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表1 がん薬物療法専門医育成のための日本臨床腫瘍学会の活動

1993年	8月26日	第1回日本臨床腫瘍研究会開催(名古屋・有吉 寛会長)
2002年	3月2日	日本臨床腫瘍学会(任意団体)設立，臨床腫瘍専門医制度の制定
2003年	2月28日-3月1日	第1回日本臨床腫瘍学会総会開催(福岡・桑野信彦会長)
	8月23日-24日	第1回教育セミナーAセッション開催(東京)
	11月28日	臨床腫瘍学第3版出版
2004年	4月1日	暫定指導医認定(441人)
	8月2日	特定非営利活動(NPO)法人日本臨床腫瘍学会設立申請(東京都)
	11月24日	東京都よりNPO法人設立の認証
	12月15日	NPO法人の登記
2005年	3月31日	日本臨床腫瘍学会(任意団体)解散
	4月1日	特定非営利活動(NPO)法人日本臨床腫瘍学会への移行
	4月1日	暫定指導医(674人)・認定研修施設(110施設)認定
	6月11日-12日	第1回Best of ASCO in Japan開催(東京)
	6月29日	日本医学会の提言
	11月19日-20日	がん薬物療法専門医認定試験(東京)
2006年	3月18日	がん薬物療法専門医のための研修カリキュラム制定
	4月1日	がん薬物療法専門医(47人)・暫定指導医(382人)・認定研修施設(132施設)認定
	10月20日	日本専門医認定制機構入社
	10月20日	新臨床腫瘍学出版
2007年	4月1日	がん薬物療法専門医(79人)・暫定指導医(234人)・認定研修施設(32施設)認定
	8月3日	がん専門医育成のための卒前教育カリキュラム制定
2008年	2月19日	がん薬物療法専門医の広告認可
	4月1日	がん薬物療法専門医(79人)・暫定指導医(220人)・認定研修施設(34施設)認定

て順風満帆ではなかった.

日本臨床腫瘍研究会が，学会に移行し専門医制度を発足させることになった理由の一つとして，日本癌治療学会の動向があげられる．1990年代の後半に日本癌治療学会でも専門医制度制定の動きがあり，1995年に臨床腫瘍医制度検討委員会が設置された．しかし，1997年に理事会・評議員会で臨床腫瘍医制度が否決されたために，これに代わるものとして2001年より臨床試験登録医制度を発足させた．すなわち，がん治療に関する日本最大の臨床系学会である日本癌治療学会が専門医制度を制定しない旨，決議したことにより，当時の臨床腫瘍研究会内に専門医制度制定の機運が高まったといえる．しかし，その後の社会情勢の急激な変化もあり，2003年12月開催の日本癌治療学会理事会で臨床試験登録医制度から，'がん治療専門医'制度への移行が承認された．2004年の第42回日本癌治療学会総会での，がん治療専門医制度規則，施行細則の承認を経て，2005年に日本癌治療学会の'がん治療専門医'制度が発足した[2].

日本臨床腫瘍学会の'臨床腫瘍専門医'制度は，世界的レベルのmedical oncologist育成を目指す制度であり，日本癌治療学会の'がん治療専門医'制度は，現在がん治療に携わっている医師の診療レベルを底上することを目的とした制度であった．したがって，全くコンセプトの異なる制度ではあるが，国民からすると2種類の'がん専門医'が誕生することになり，極めてわかりにくいことも事実であった[3]．そのために，マスコミ，患者団体などより制度の一本化が強く求められたが，コンセプトの全く異なる制度を一つにまとめることは極めて困難であった．

この事態を解決するために，日本医学会，全国がん(成人病)センター協議会の仲裁により，日本臨床腫瘍学会，日本癌治療学会の代表による数回の話し合いがもたれた．この話し合いの結果に基づき，日本医学会が2005年6月29日

に'がん治療専門医をめぐっての提言'を公表した．提言の主な内容は，①がん治療認定医制を設ける，②がん治療認定医制に関する共通のカリキュラムを3学会(日本癌学会，日本癌治療学会，日本臨床腫瘍学会)が中心となって作成する．その認定も3学会共通で行う．具体的な方策は3学会で合同委員会を設けて協議する．庶務的業務を日本癌治療学会が取り扱う，③がん治療に関しては，認定医と専門医の2段階制とする，となっている．

この一連の過程で，日本臨床腫瘍学会の専門医は'臨床腫瘍専門医'から'がん薬物療法専門医'に名称が変更された．また，日本癌治療学会の'がん治療専門医'は，日本癌治療学会，日本癌学会，日本臨床腫瘍学会および全国がん(成人病)センター協議会の4組織で，中間法人日本がん治療認定医機構(http://www.jbct.jp/)を設立し，'がん治療認定医'として2007年度より認定が開始されている．

2. がん薬物療法専門医

日本臨床腫瘍学会のがん薬物療法専門医に求められる能力は，①薬物療法に関する十分な基礎知識がある，②標準的治療が正しく実施できる，③癌化学療法に伴う副作用に適正に対処できる，④EBM創生のための臨床試験が実施できる，⑤緩和医療ができる，⑥がん治療に関するセカンドオピニオンができること，などである．日本臨床腫瘍学会の教育カリキュラム(http://jsmo.umin.jp/senmoni/cal.html)は，2004年に発表されたASCO/ESMOのグローバルコアカリキュラムに若干の修正を加えたものであり，世界的レベルのmedical oncologistを育成するためのものである[4,5]．

専門医認定のための条件として，①会員歴2年以上，②2年の初期研修後に5年以上のがん治療の臨床研修，③認定研修施設での所定の研修カリキュラムに基づく2年以上の研修，④各科基本学会(日本内科学会など)の認定医・専門医資格取得，⑤臨床腫瘍学の論文1編以上，日本臨床腫瘍学会での発表1回以上，⑥教育セミナー出席，⑦過去5年以内の30例の症例報告書提出，⑧専門医認定試験合格，となっている．

がん薬物療法専門医認定試験は，30例の病歴査読，筆記試験，面接試験の3段階で実施されている．病歴査読は，基本的ミスの有無，症例選択の適切さとバランス，診断名は適切か，病歴・入院時現症・検査などは適切か，問題点の取り上げ方は適切か，入院後経過，特に全身的治療，化学療法について適切に記載されているか，考察は対象分野に的を当てて，EBMを考慮して文献なども含めて適切に記載されているか，の各項目が減点法で評価される．2人の査読者が採点を行い，2人ともに，60点未満と判断した場合には，専門医制度委員会委員長の最終判断で病歴査読が不合格とされる場合がある．病歴査読で不合格となった場合には，筆記試験・面接試験は受験できない．

筆記試験・面接試験は2日間連続で実施され，1日目が筆記試験である．筆記試験の問題は，年2回実施している教育セミナー(A・Bセッション)と新臨床腫瘍学に記載してある内容を中心に出題される．教育セミナーはAセッション2日間，Bセッション1日，合計3日間で臨床腫瘍学の総論・各論をすべてカバーする構成になっている．なお，2005年3月に開催された第4回教育セミナー以降の内容はホームページ上(http://jsmo.umin.jp/seminar_slide.html)で音声付スライドとして公開されている．筆記試験の内訳は，基礎腫瘍・臨床腫瘍総論，各臓器腫瘍，支持療法・緩和医療であり，各臓器腫瘍では，消化管，呼吸器，乳房などから，婦人科，泌尿器，皮膚癌，小児腫瘍まで幅広く出題されている[6]．

2日目に面接試験が行われているが，面接試験は1人の受験者に対して2-3人の試験官で実施している．まず，提出された30例の病歴要約の中から試験官が指定した1症例の病歴要約を受験者が5分程度で説明し，それに対して試験官が関連する質問をする形式で試験が実施される．面接試験に際しては，病歴要約を適切に記載していることが非常に重要である．面接試験で，臨床腫瘍学に対する理解が不十分と判断

表2 日本臨床腫瘍学会のがん薬物療法専門医・暫定指導医・認定研修施設認定数の推移

年度	暫定指導医	認定研修施設	がん薬物療法専門医
2003年度	441人(450人申請)	—	—
2004年度	674人(710人申請)	110施設(125施設申請)	—
2005年度	382人(402人申請)	132施設(132施設申請)	47人(55人申請)
2006年度	234人(267人申請)	32施設(33施設申請)	79人(101人申請)
2007年度	220人(245人申請)	34施設(37施設申請)	79人(132人申請)
合計	1,951人	308施設	205人

された場合には，筆記試験の点数にかかわらず不合格と判定される場合がある．

2003年度より暫定指導医の認定，2004年度より認定研修施設の認定が，それぞれ開始されている．がん薬物療法専門医の認定試験は，2005年度より毎年実施されており，2008年4月1日現在で205人が，がん薬物療法専門医に認定されている(表2)．2008年2月19日には，専門医広告も可能となっており，社会的にも認知されるようになった．しかし，現在の専門医数は我が国で必要とされる専門医数と比較すると大きく不足しており，今後も専門医育成の努力を継続する必要がある．

3. その他の教育・啓発活動

a. がん専門医育成のための卒前教育カリキュラム

がん専門医を効率良く育成するには，卒前からの系統だった臨床腫瘍学の教育が重要である．しかし，現在のモデルコアカリキュラムでは，臨床腫瘍学の教育内容が十分とは言い難い．日本臨床腫瘍学会では，モデルコアカリキュラムの内容を補う目的で，平成16-18年度厚生労働科学研究費補助金がん臨床研究事業'効果的かつ効率的ながん専門医の育成方法に関する研究'班(主任研究者：大江裕一郎)で作成した'効果的かつ効率的ながん専門医育成のための卒前教育カリキュラム'を基に，教育委員会(委員長：原田実根)で議論し，'日本臨床腫瘍学会がん専門医育成のための卒前教育カリキュラム' (http://jsmo.umin.jp/senmoni/cal.html)を作成した．全国の医学部・医科大学に徐々にではあるが腫瘍内科，臨床腫瘍学などの講座が設置されており，卒前教育が更に充実することを期待したい．

b. 新臨床腫瘍学

日本臨床腫瘍学会では，研究会時代より臨床腫瘍学の教科書を編集，出版している．1996年7月に'臨床腫瘍学，第1版，癌と化学療法社(東京)'が出版された．'臨床腫瘍学'の編集方針としては，3-4年に1回全面改訂を行う，著者の恣意的な内容にならないようレビューアー制度を設け客観的評価を行う，世界的現状をレビューし自らのデータのみに固執しないようにして自画自賛のレビューを排除する，などである．第2版は1999年2月，第3版は2003年11月に，それぞれ出版されている．2006年10月には出版社を南江堂に変更して，現在の'新臨床腫瘍学'が出版された．'新臨床腫瘍学'でも'臨床腫瘍学'の編集方針は引き継がれており，各項目に対する個々のレビューアー制度はなくなったものの，日本臨床腫瘍学会教育委員会のメンバーが編集委員としてすべての内容を評価し，必要に応じて執筆者に改訂を依頼している．したがって，内容の重複を避け，全体的に統一された構成となっている．

c. Best of ASCO in Japan

日本臨床腫瘍学会では，教育セミナーの上級コースとしてASCO(米国臨床腫瘍学会)と共同で，2005年よりBest of ASCO in Japanを開催している．Best of ASCO in Japanは2日間にわたり，その年のASCOで発表された優れた演題

表3 日本臨床腫瘍学会の教育・啓発活動

がん薬物療法専門医のための研修カリキュラムの制定
がん薬物療法専門医・暫定指導医・認定研修施設の認定
教育セミナーA・Bセッションの開催およびWeb上の公開
Best of ASCO in Japanの開催
新臨床腫瘍学の出版
がん専門医育成のための卒前教育カリキュラムの制定
コメディカルのための教育セミナー開催
市民公開講座の開催

を，分野ごとに国内外のトップレベルの研究者が研究の背景・位置づけ・解釈などを解説し討論するものである．ASCOに参加しても，全領域にわたり重要な演題を把握することは極めて難しく，ASCO参加者の出席も多い．

d. コメディカルに対する教育セミナーと市民公開講座

その他の教育・啓発活動としてコメディカルを対象とした教育セミナー，市民公開講座なども実施している．日本臨床腫瘍学会会員の約90％が医師であるが，残りの10％は，薬剤師，看護師，治験コーディネータ，企業関係者などで占められている．がん薬物療法専門医のための教育セミナーへの医師以外の参加も少なくなく，コメディカルに対する教育も非常に重要である．学術総会に合わせて会長の判断で，コメディカルに対する教育セミナーも開催されている．

おわりに

日本臨床腫瘍学会は2003年2月に開催された第1回日本臨床腫瘍学会総会の際には，会員数わずか750人の小規模な学会であったが，現在では7,000人を超える会員数にまで成長している．学会設立の目的の一つが，臨床腫瘍医(Medical Oncologist)の育成であり，学会としては教育活動に重きを置いており，表3に示すように多岐にわたる教育・啓発活動を学会として実施している．ただし，学術集会でのオリジナルデータの発表が少ないとの批判が一部にあることも事実であり，今後の検討課題である[7]．2002年3月より準備を始めた日本臨床腫瘍学会の専門医制度も，2005年度よりがん薬物療法専門医の認定を開始し，社会的に認知され，軌道に乗りつつある．しかし，専門医の絶対数は大幅に不足しており，これからも学会としての教育育成活動を推進していくことが重要である．

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Prolonged neutropenia after dose-dense chemotherapy with pegfilgrastim

In the dose-dense (DD) chemotherapy trial result reported by Piedbois et al. [1], they found more hematological toxicity leading to treatment discontinuation in the pegfilgrastim supported DD chemotherapy arm. The manufacturer's product information for pegfilgrastim indicates that it should be used once per chemotherapy cycle and should not be used in the period between 14 days before and 24 h after administration of cytotoxic chemotherapy, which is not practically possible in DD chemotherapy. Although pegfilgrastim has not been approved in Japan, we observed an episode of prolonged neutropenia in a Japanese patient who had undergone DD doxorubicin plus cyclophosphamide (AC) neo-adjuvant chemotherapy in the United States before being referred to us to continue chemotherapy then perform resection.

She was a 48-kg female in her mid-30s who presented at the Ithaca Medical Group clinic (New York) with locally advanced breast cancer. She underwent four cycles of DD AC, with pegfilgrastim 6 mg s.c. on day 2 of each cycle. Her absolute neutrophil count (ANC) was 2350/mm^3, 3650/mm^3, 4150/mm^3, and 7300/mm^3 at the start of the each cycle. After the forth AC cycle, she was referred to us for further chemotherapy. ANC at day 20 of the forth AC cycle was 3300/mm^3 but decreased to 500/mm^3 on day 26. Therefore, we had to postpone chemotherapy. Two weeks later (1 week after the last dose of filgrastim), the patient's ANC recovered to 1500/mm^3 and she received the first cycle of docetaxel (100 mg/m^2). She had received a total of 14 administrations of filgrastim starting from day 3 of the first cycle of docetaxel and had been severely neutropenic from day 7 (300/mm^3) to day 22 (300/mm^3). Her ANC on days 29 and 36 were 600/mm^3 and 1100/mm^3, respectively. Due to prolonged neutropenia, we decided to proceed to surgery. The patient has completed weekly paclitaxel as adjuvant chemotherapy, begun 3 months after the last docetaxel, with no major hematological toxicity.

Serum pegfilgrastim remained elevated in some patients even 14 days after the administration [2] and this seems dependent on weight-adjusted dose [3]. Chemotherapy administration during this period may very well cause more bone marrow suppression. It is possible that a 6-mg dose of pegfilgrastim is too large for Japanese patients in general. In our patient, the elevated ANC (3300/mm^3) on day 20 and grade 4 neutropenia on day 26 suggests that the effect of pegfilgrastim lasted at least 3 weeks. We therefore caution against the routine use of pegfilgrastim in DD chemotherapy until an optimal dose in this setting is ascertained, especially for low-weight patients. We strongly recommend that the European Society of Medical Oncology warns oncologists against the routine use of pegfilgrastim in DD chemotherapy, which is not an indication approved, and in which situation the drug has never been formally tested for optimal dosage. Such a recommendation would be particularly effective if made through the *Annals of Oncology*, given that this journal is well known and influential publication for clinical oncologists worldwide.

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EPIDEMIOLOGY

Economic evaluation of 21-gene reverse transcriptase-polymerase chain reaction assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer in Japan

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Abstract The 21-gene reverse transcriptase-polymerase chain reaction assay with a patented algorithm is validated as a good predictor of prognosis and potential benefit from adjuvant chemotherapy for lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer, while its high cost raises concern about how to finance it. Cost-effectiveness analysis comparing prevalent National Comprehensive Cancer Network (NCCN) guideline/St Gallen recommendation-guided treatment with the assay-guided treatment is carried out with budget impact estimation in the context of Japan's health care system. Incremental cost-effectiveness ratios are estimated as 2,997,495 ¥/QALY (26,065 US$/QALY) in the comparison between NCCN guided-treatment vs. the assay-guided treatment, and as 1,239,055 ¥/QALY (10,774 US$/QALY) in the comparison between St Gallen guided-treatment vs. the assay-guided treatment. Budget impact is estimated as ¥2,638 million (US$23 million) to ¥3,225 million (US$28 million) per year. The routine use of the assay is indicated as cost-effective. And the budget impact could be judged as within fundable level.

Keywords Breast cancer · Budget impact · Cost-effectiveness · Gene diagnosis · 21-gene signature · Tailor-made medicine

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Introduction

In recent years, the medical profession as well as the general public have become to have high hopes for the future of "tailor-made medicine", which means individualised treatment according to each patient's pathology, especially using gene diagnoses or biomarkers [1]. And this is the case with cancer care in Japan, as well [2].

Regarding breast cancer care, the role of adjuvant chemotherapy for lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer (LN−, ER+, ESBC) in order to prevent or delay distant recurrence after primary surgery has been debated [3–6], while the use of hormonal therapy with tamoxifen or aromatase inhibitors in those cases is established by several large randomised clinical trials [7, 8]. Efforts to aggregate available evidences have been made in order to best guide the clinical decision of whether to add chemotherapy or not, which result in the development of consensus guidelines, such as National Comprehensive Cancer Network (NCCN) guideline [9, 10] or St Gallen recommendation [5]. These guidelines evaluate patient's risk of recurrence based on factors such as age, tumour size and histology, and then suggest the indication for adjuvant chemotherapy to higher risk patients

based on a judgement that the benefit of survival from chemotherapy overweighs the disbenefit of adverse effects and medical risks [11]. However, the risk classification which underlies this judgement has been considered as not certain nor specific enough, so that it leaves a room for the development of a more accurate and individualised predictor of the risk of recurrence.

A multigene assay of resected breast cancer tumour tissue was implemented in order to realise more informed and individualised decision for adjuvant chemotherapy indication, which resulted in the development of the 21-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assay with a patented algorithm (Oncotype DX® Breast Cancer Assay). It gives an individual case of LN−, ER+, ESBC Recurrence Score (RS) that represents individualised risk of recurrence. The accuracy of RS as criteria in assessing the risk of recurrence was validated by a prospective study of historical clinical trial data from National Surgical Adjuvant Breast Cancer Project (NSABP) B-14 study with the gene assay of preserved tumour tissue [12]. Furthermore, the accuracy of RS in predicting the magnitude of chemotherapy benefit was validated by a similar study including data from NSABP B-20 study with the gene assay [13]. In other words, patients classified as high risk of recurrence by RS criteria are likely to be highly responsive to chemotherapy, which implies that the assay is clinically efficient in identifying those who could benefit from adjuvant chemotherapy.

This development is deemed as a pathway geared towards tailor-made medicine in breast cancer care, which anticipates a similar innovative assay like 70-gene signature (MammaPrint®) [14]. Yet another significant characteristic of the 21-gene RT-PCR assay is its high price, ¥450,000 (US$3,913; US$1 = ¥115), while the reimbursement for a conventional gene diagnosis test of malignant tumour is set at ¥20,000 (US$174) in the social health insurance system of Japan. Needless to say, a valuable innovation of technology deserves patent protection and accompanying financial rewards as its own right. However, from the viewpoint of economics, it is imperative to appraise the "value for money" of such highly priced new technology [15]. The proportion of LN−, ER+ cases among breast cancer is large, 28.7% [16], and the incidence of breast cancer is estimated as 41,494 in 2005 and increasing continuously [17]. Therefore, once the assay becomes a standard procedure within social insurance benefit package, more than 12,000 assays are expected to be implemented in a year. This leads to a concern about its implication for health financing. From the viewpoint of health manager, it is also imperative to appraise the "budget impact" [18], which basically correlates to the product of the price and the quantity of health services provided.

To date, there are two studies that look at economic aspects of the 21-gene RT-PCR assay based on validation studies in the U.S. health system. Hornberger et al. carried out an economic evaluation of the assay, and reported it as cost-saving based on a reclassification of patients' risk using RS criteria, instead of NCCN criteria [19]. Lyman et al. also reported that RS-guided treatment could be cost-saving compared to the treatment with tamoxifen combined with chemotherapy for all patients, and cost-effective compared to the treatment with tamoxifen alone for all patients [20]. There is no report from any other countries nor yet a comparison with St Gallen-guided treatment.

This study aims to evaluate cost-effectiveness and budget impact of the 21-gene RT-PCR assay in Japan's health care system. The results should be useful in considering the diffusion of the assay in Japan, and could inform health care policy in the era of tailor-made medicine in developed countries.

Methods

We conduct a cost-effectiveness analysis with decision trees and Markov modelling based on the validation studies of the 21-gene RT-PCR assay [12, 13, 21], and a costing under Japan's social health insurance system including a sensitivity analysis from societal perspective. We also estimate the budget impact of the assay on Japan's social health insurance system based on our economic model.

Scenarios and comparisons

Both Japanese clinical practice [22] and consensus guidelines [23, 24] are in accordance with NCCN guideline as well as St Gallen recommendation in a mixed way. And changing criteria from NCCN/St Gallen to RS in risk reclassifications with estimated distant recurrence free survival in 10 years ($DRFS_{10}$) were reported in one of the validation studies as shown in Table 1 [21]. (Since $DRFS_{10}$ of patients with intermediate risk according to St Gallen criteria was not yet published, we assume the mid-value of $DRFS_{10}$ between high risk and low risk classified by St Gallen criteria.) Three scenarios are set up in this study: a hypothetical cohort of LN−, ER+, ESBC at the age of 55 undergoes NCCN-guided treatment, St Gallen-guided treatment, and RS-guided treatment. The age of 55 is chosen according to the average age of equivalent patient population in a nationwide cancer registry [16]. The former two scenarios intend to depict the status quo of Japanese practice to some extent. The last scenario intends to illustrate the situation in which the 21-gene RT-PCR assay is applied routinely.

Table 1 Risk reclassification by the 21-gene RT-PCR[a] assay with expected $DRFS_{10}^{b}$

			Recurrence Score criteria		
			High risk	Intermediate risk	Low risk
NCCN[c] criteria	High risk	Probability	29%	22%	49%
		$DRFS_{10}$	0.70	0.86	0.92
		Range tested in sensitivity analyses	Change by ±50%	Change by ±50%	Change by ±50%
	Low risk	Probability	6%	22%	72%
		$DRFS_{10}$	0.57	0.82	1.00
		Range tested in sensitivity analyses	Change by ±50%	Change by ±50%	Change by ±50%
St Gallen criteria	High risk	Probability	36%	22%	42%
		$DRFS_{10}$	0.67	0.82	0.92
		Range tested in sensitivity analyses	Change by ±50%	Change by ±50%	Change by ±50%
	Intermediate risk	Probability	16%	23%	61%
		$DRFS_{10}$	0.62[d]	0.82[d]	0.96[d]
		Range tested in sensitivity analyses	Change by ±50%	Change by ±50%	Change by ±50%
	Low risk	Probability	6%	22%	72%
		$DRFS_{10}$	0.57	0.82	1.00
		Range tested in sensitivity analyses	Change by ±50%	Change by ±50%	Change by ±50%

Source: Reference [21]

[a] Reverse transcriptase-polymerase chain reaction

[b] Distant recurrence free survival in 10 years

[c] National Comprehensive Cancer Network

[d] Assumed as the mid-value of $DRFS_{10}$ between high risk and low risk classified by St Gallen criteria

Regarding the use of adjuvant chemotherapy, 100% of patients classified as high risk by NCCN/St Gallen criteria and 50% of patients classified as intermediate risk by St Gallen criteria are assumed to undergo chemotherapy, while 100% of patients classified as high or intermediate risk by RS criteria are assumed to undergo chemotherapy.

Then, the two pairs of scenarios are compared: NCCN-guided treatment vs. RS-guided treatment, and St Gallen-guided treatment vs. RS-guided treatment. These comparisons intend to depict the diffusion of the assay in Japanese practice. The use of chemotherapy decreases from 92 to 49% under the former comparison, and from 75 to 49% under the latter comparison by the adoption of RS criteria.

Decision tree and Markov model

We construct decision trees with Markov model of clinical courses followed by LN−, ER+, ESBC patients, which is shown in Fig. 1.

The decision tree 1 shows the comparison between NCCN-guided treatment vs. RS-guided treatment; and the decision tree 2 shows the comparison between St Gallen-guided treatment vs. RS-guided treatment. Decision nodes of these trees are as to a decision whether to apply the 21-gene RT-PCR assay or not. Following chance nodes discern the cohort to different adjuvant therapies depending on the risk classification and human epidermal growth factor receptor type2 (HER2) status. Since the use of trastuzumab for HER2 positive (HER2+) cases as adjuvant therapy is about to be included in the social health insurance benefit according to the results of international clinical trials [25, 26], we set up three types of adjuvant therapies: hormonal therapy (HT), HT plus chemotherapy (CT), and HT plus CT plus trastuzumab. Branches with CT lead to subtree B via a chance node, which discern the cohort to different toxicities.

The Markov model shows the clinical course once the adjuvant therapy is completed. Five stages are modelled here: (1) LN−, ER+, ESBC after criteria-guided adjuvant therapy; (2) Distant recurrence with response to treatment; (3) Distant recurrence with no response to treatment; (4) Progression of disease after distant recurrence; and (5) Death. Transitions between the stages are indicated with arrows. Patients follow various courses after recurrence, so conditions other than these five stages and transitions not described with arrows here are possible. However, we model the course in this way based on available reports of prognosis model of metastatic breast cancer, which is calibrated with the results of several randomised trials [19, 27]. Patients with recurrence undergo drug treatment with HT, CT, and/or trastuzumab depending on their status.

The span of each stage is set up at 1 year. Markov process is repeated up to 10 years, since the transitional probabilities of recurrence are calculated from $DRFS_{10}$ and

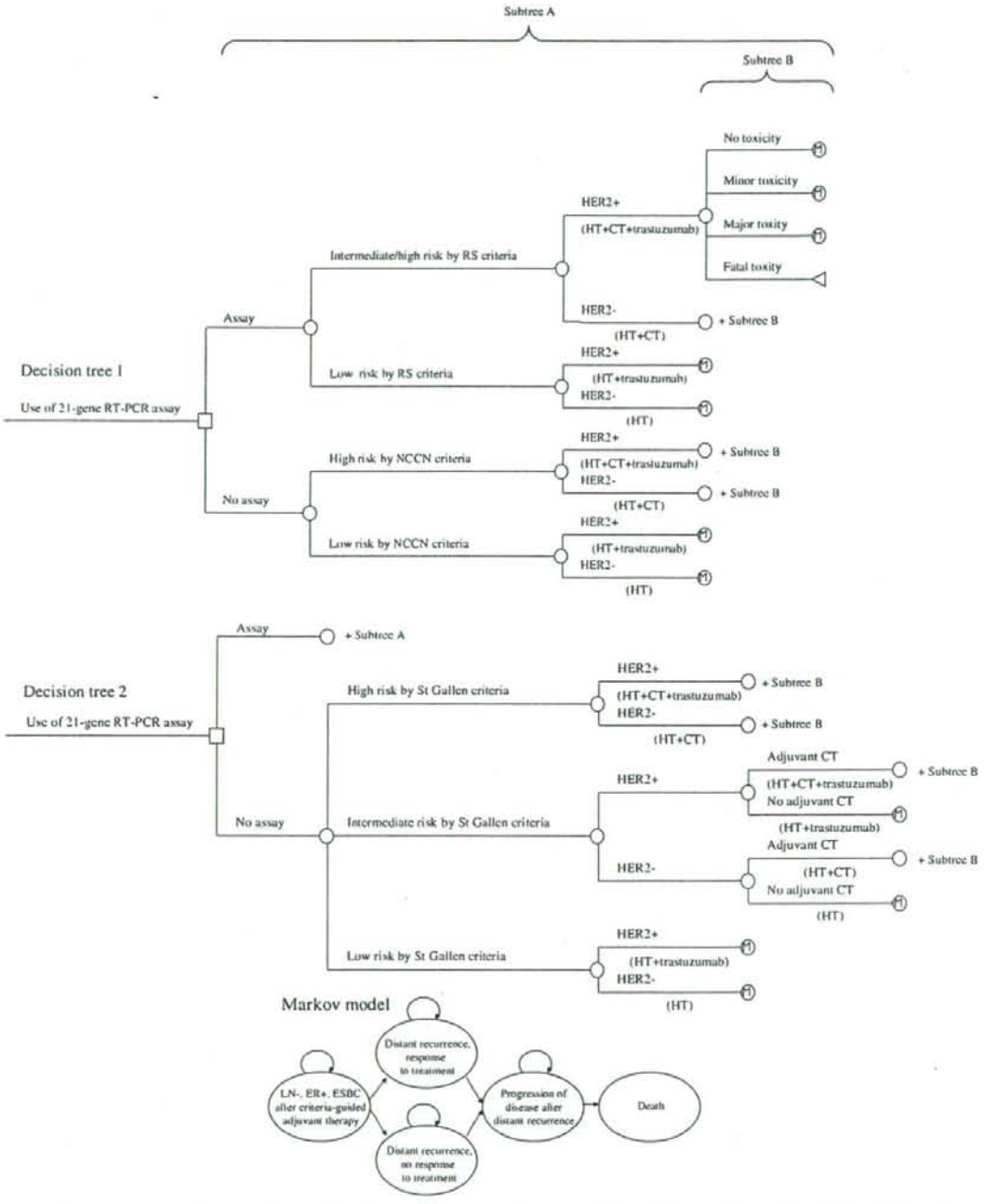

Fig. 1 Decision tree and Markov model. Abbreviations: Reverse transcriptase-polymerase reaction (RT-PCR), recurrence score (RS), human epidermal growth factor receptor type2 (HER2), hormonal therapy (HT), chemotherapy (CT), National Comprehensive Cancer Network (NCCN), lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer (LN−, ER+, ESBC)

most of recurrences are expected to occur within this time horizon. After the 10-year, survived patients without recurrence are assumed to have a life expectancy for Japanese female at age 65 [28], and those with recurrence are to have a life expectancy of 2 years.

Outcome estimation

Outcomes by the scenario in terms of years of life saved (YOLSs) and quality adjusted life years (QALYs) are estimated by assigning probabilities and utility weights to the decision trees and Markov model from the literature.

Probabilities of risk classification, attached to the first chance nodes of each branch, are adopted from one of the validation studies of the 21-gene RT-PCR assay [21] shown in Table 1. Table 2 shows the other probabilities and utility weights used. A probability of HER2+, 9.3%, attached to the second chance nodes, is adopted from a nationwide breast cancer registry [16]. Probabilities of adjuvant chemotherapy toxicity, attached to the chance node in the subtree B, are assumed to be 60% for minor toxicity, 5% for major toxicity and 0.5% for fatal toxicity from a report of efficacy and cost-effectiveness of adjuvant chemotherapy in breast cancer [29].

Regarding the Markov model, transitional probabilities of recurrence with adjuvant HT are calculated from $DRFS_{10}$ in Table 1. The effectiveness of adding adjuvant CT and trastuzumab are incorporated as risk reduction of recurrence. Relative risk reductions resulted from CT among patients classified as high risk and intermediate risk by RS criteria are fixed at 74 and 39%, respectively, which are adopted from one of the validation studies of the 21-gene RT-PCR assay [13]. A relative risk reduction resulted from trastuzumab among HER2+ patients are assumed to be 36% for up to 2 years according to the results of clinical trial [26]. As mentioned earlier, transitional probabilities between stages after recurrence are adopted from prognosis model of metastatic breast cancer [19, 27]. It is assumed that the response to treatment and the prognosis after recurrence differ depending on HER2 status. Probabilities of the response to treatment for recurrence are fixed at 38.0% among HER2− patients and 54.0% among HER2+ patients [27]. Probabilities of the progression of disease after recurrence are also fixed at: 59.7% if HER2− and having responded to treatment, 53.7% if HER2+ and having responded to treatment, 98.3% if HER2− and not having responded to treatment and 88.5% if HER2+ and not having responded to treatment [19]. Probabilities of death after the progression of disease are fixed at 40.0% among HER2− patients and 37.2% among HER2+ patients [19].

In order to estimate the outcome in terms of QALYs, utility weights are chosen for various health statuses during the clinical course which patients follow. A weight for health status after adjuvant therapy without any toxicity or distant recurrence is chosen to be 0.98 [30]. Weights for toxicities are 0.90 for minor toxicity, and 0.80 for major toxicity [29], of which duration is assumed as 6 months. Health status during chemotherapy against the distant recurrence or the progression of disease weighs 0.50 [31], of which duration is assumed as 6 months. Health statuses after the chemotherapy weigh 0.84 if responded, 0.70 if stable and 0.49 if progressive [27].

Outcome is discounted at a rate of 3% [32].

Costing

From societal perspective, costing should cover the opportunity cost borne by various economic entities in the society. In the context of this study, costs borne by social insurers and patients are considered, since these two entities are major payers to health care providers under Japan's social health insurance system. The amount of direct payments by these entities, mostly according to the national medical care fee schedule, are estimated as costs, while costs to sector other than health and productivity losses are left uncounted in this study. This choice of scope in costing allows the following budget impact estimation.

Cost items are identified along the decision trees and Markov model: the 21-gene RT-PCR assay, adjuvant therapies, treatments for toxicity, monitorings, treatments for distant recurrence, and end-of-life treatments as shown in Table 3. As already mentioned, the cost of the assay is ¥450,000 (US$3,913), according to the price offered by Japanese supplier of Oncotype DX® Breast Cancer Assay. Costs of treatments except the end-of-life treatments are estimated by combining a model of breast cancer care and the national medical care fee schedule. The care model is developed based on both a nationwide survey of Japanese expert practice [22] and consensus guidelines [23, 24].

Adjuvant hormonal therapy includes outpatient care with tamoxifen, aromatase inhibitors, and LH–RH analogues depending on patient's status, and is assumed to continue up to 5 years, which costs ¥534,610 (US$4,649) per year. Adjuvant chemotherapy includes various regimens. Anthracycline-based combination chemotherapy is used for about half of the cases, and oral fluorinated pyrimidine and CMF (cyclophosphamide, methotrexate and 5-fluorouracil) therapy are frequently used among other regimens. These cost ¥343,001 (US$2,983). Adjuvant trastuzumab costs ¥3,105,120 (US$27,001) per year, of which administration is assumed to continue for 1 year.

There are three levels of toxicity in the decision tree. However, only the cost of major toxicity is estimated as ¥173,352 (US$1,507), which includes unplanned 1 month

Table 2 Probabilities and utility weights

	Base case value	Range tested in sensitivity analyses	Source
Probabilities			
Patient status			
HER2[a]+	9.3%	Change by ±50%	[16]
Adjuvant chemotherapy toxicity			
Minor	60.0%	Change by ±50%	[29]
Major	5.0%	Change by ±50%	[29]
Fatal	0.5%	Change by ±50%	[29]
Relative risk reduction of distant recurrence			
Chemotherapy			
Intermediate risk classified by RS[b] criteria	39.0%	Change 0–76%	[13]
High risk classified by RS criteria	74.0%	Change 47–87%	[13]
Trastuzumab	36.0%	Change 24–46%	
(Duration)	(2 years)	Change to 5 years	[26]
Response to treatment for distant recurrence			
HER2−	38.0%	Change by ±50%	[27]
HER2+	54.0%	Change by ±50%	[27]
Progression of disease after distant recurrence			
HER2−, response to treatment	59.7%	Change by ±50%	[19, 27]
HER2−, no response to treatment	98.3%	Change by ±50%	[19, 27]
HER2+, response to treatment	53.7%	Change by ±50%	[19, 27]
HER2+, no response to treatment	88.5%	Change by ±50%	[19, 27]
Death after progression of disease			
HER2−	40.0%	Change by ±50%	[19, 27]
HER2+	37.2%	Change by ±50%	[19, 27]
Utility weights			
After adjuvant therapy without distant recurrence	0.98	Change by ±20%	[30]
Toxicity			
Minor	0.90	Change by ±20%	[29]
Major	0.80	Change by ±20%	[29]
Distant recurrence			
Chemotherapy, 6 months only	0.50	Change by ±20%	[31]
Response to treatment	0.84	Change by ±20%	[27]
Stable	0.70	Change by ±20%	[27]
Progression of disease	0.49	Change by ±20%	[27]

[a] Human epidermal growth factor receptor type2

[b] Recurrence Score

hospitalisation in two-fifths of the cases and rescue treatment at outpatient clinic in three-fifths of the cases [33, 34]. The cost of minor toxicity, from which 60% of patients suffer, is included in the cost of adjuvant chemotherapy, since prophylactic use of antiemetic, for example, is applied routinely these days. And the clinical course of fatal toxicity is diverse and not fit to costing by modelling here, so its cost is estimated later coupled with the cost of end-of-life treatment.

Patients who complete adjuvant therapy are assumed to visit a clinic twice a year for the purpose of monitoring, which costs ¥25,340 (US$220) per year.

There are various options of treatments for the distant recurrence depending on regimens used in adjuvant therapy. Yet, we assume crossover hormonal treatments followed by capecitabine within the first year as typical first line and second line therapies for our hypothetical cohort, which cost ¥558,458 (US$4,856) per year. We further assume that this cost is applicable to second year and afterwards. For HER2+ patients, trastuzumab is additionally administered, of which cost is the same as one during the adjuvant therapy.

The end-of-life treatments are diverse in contexts and lack consensus guidelines or survey data. Its practice