taxane may be added for some patients and additionally, trastuzumab is included for HER-2-positive patients. Indeed, the percentage of patients who experienced pCR increased when an anthracycline was added to their treatment regimens, and further increased with the addition of a taxane [1, 2]. With NC, limited surgery is assumed to be performed after the volume of the advanced breast cancer tumor is reduced, whereas NC is designed to extend the survival of patients by causing tumors to disappear solely by using anticancer drugs. Therefore, even those patients with breast cancer who have relatively small tumors close to their early-stage are currently treated first with anticancer drugs. Although preoperative chemotherapy has been used in wider range of cases, there are no practical criteria for its indications in terms of the results from clinicopathological examinations. Clinically, some patients show excellent responses to anticancer drugs and NC should be performed proactively, whereas other patients do not significantly benefit from these drugs and NC may not be necessary. Thus, individually predicting the efficacy of NC used for different purposes and deciding whether it should be performed is a current clinical goal.

In recent translational research, the efficacy of anticancer or hormone drugs were predicted by immunologically examining the sensitivity of the patients to these drugs [3]. As the indications of NC continue to expand, it is necessary to precisely select therapeutic methods, including the type of anticancer drugs, based on small tissue samples and laboratory test results that are available before surgeries. In the present study, we retrospectively examined cases treated at our clinic to determine whether it is possible to predict the efficacy of NC used for different purposes based on pretreatment tissue samples and the tumor shape observed using pretreatment CT imaging.

Methods

Patients and treatments

All patients diagnosed with operable breast cancer and treated between May 1998 and July 2006 at the National Cancer Center Hospital (NCCH; Tokyo, Japan) with NC, including an anthracycline and a taxane, were included this retrospective study. NC was indicated for clinical stage II tumors and tumors >3 cm or stage III breast cancer tumors. Core-needle biopsy was performed before NC to allow a pathological diagnosis. Doxorubicin (DOX, 50 mg/m^2) and docetaxel (DOC, 60 mg/m^2) (AT regimen) were administered in four cycles every 3 weeks before surgery. Additional adjuvant treatment with DOX/DTX was given if the patients achieved complete or partial remission after preoperative chemotherapy or were otherwise treated with four cycles of intravenous cyclophosphamide, methotrexate, and 5-fluorouracil. FECT treatment was four cycles of 5-fluorouracil (500 mg/m^2)/epirubicin (100 mg/m^2)/cyclophosphamide (500 mg/m^2) plus 12 weekly cycles of paclitaxel (80 mg/m^2) followed by surgery. The ACT regimen was 4 cycles of doxorubicin (60 mg/m^2)/cyclophosphamide (600 mg/m^2) plus 12 weekly cycles of paclitaxel (80 mg/m^2) followed by surgery. The T regimen was 12 weekly cycles of paclitaxel (80 mg/m^2) followed by surgery. Recently, patients with breast cancer that showed an HER-2 overexpression phenotype have received trastuzumab as PST. However, in this study we excluded these patients because we have only recently begun to use trastuzumab, and many HER-2–positive patients did not receive this treatment. Tamoxifen (20 mg/day) or anastrozole (10 mg/day) was administered for 5 years when pretreatment biopsy specimens or surgical postchemotherapy specimens were positive for estrogen receptor (ER) or progesterone receptor (PgR). The surgical treatment employed was mastectomy or breast-conserving surgery with axillary lymph node dissection (level 2) and that was decided from both of preoperative general diagnosis (palpation, MMG, US, and MDCT findings) and intraoperative pathological findings.

Evaluation of pathological factors

Pretreatment diagnoses were established by our pathologists using a core-needle biopsy or a surgical resection. The expression levels of hormone receptors and HER-2 were determined by using immunohistological examinations. Surgical specimens were sectioned to an approximately 7–10-mm thickness and pathologically classified by pathologists. Pathologic features were noted and invasive ductal carcinomas (IDCs) were classified as one of three subtypes (papillotubular, solid-tubular, and scirrhous) according to the General and Pathological Recording of Breast Cancer guideline established by the Japanese Breast Cancer Society [4]. The diagnosis of invasive lobular carcinoma was based on tumor histology showing the absence of E-cadherin by immunohistological examination on the pretreatment specimens. The criteria for histological grading of IDCs were based on a modification of those recommended by the World Health Organization [5, 6]. The response criteria used in this study include Fisher's system [7]; pCR means no histological evidence of invasive tumor cells (specimens with only noninvasive cells were included), whereas pINV indicated the presence of invasive tumor cells. The criterion for ER- and PgR-positive samples was specific signals in more than 10% of the cancer cell nuclei, regardless of intensity. HER-2 positivity was defined as 3+ , i.e., markedly positive in more than 10% of the cancer cells.

Clinical responses to preoperative chemotherapy were reflected by the two greatest perpendicular diameters (before each chemotherapy treatment and before surgery) of tumors in the breast and an axillary lymph node. No clinical evidence of palpable tumor in the breast and axillary lymph nodes was defined as a clinical complete response (cCR). Reduction in the total tumor size by 30% or more was graded as a clinical partial response (cPR). An increase in the total tumor size of more than 20% or appearance of new suspicious ipsilateral axillary adenopathy was considered progressive disease (cPD). Tumors that did not meet any of the criteria for response or progression were considered unchanged (cNC).

CT imaging

CT examinations were performed with the patient in the supine position using a helical CT scanner (X-Vigor; Toshiba Medical Systems, Japan) between January and June 2000 or using an MDCT scanner (Aquilion, Toshiba) beginning in July 2000. The first noncontrast-enhanced CT scan served as the baseline with scanning performed from the cranial end of the sternum to the inframammary fold. Subsequently, an enhanced zoomed scan was obtained to visualize the entire breast. A bolus of 100 ml of nonionic contrast material (300 mgI/ml) was injected intravenously at a rate of 3 ml per second via an antecubital vein on the side opposite the affected breast using an automated injector. Image acquisition was started 40 s after the start of the bolus injection. The reconstruction interval was 5 mm. The tumor shape was classified into two types: localized tumors visualized as single lesions and nonlocalized tumors, including those with surrounding lesions, multiple lesions, or glandular spreading (Fig. 1). CT imaging was used before both NC and surgery. The maximum tumor size measurements and the tumor shape classification were obtained using the CT images and compared with the size measured during the pathological examination.

Results

From May 1998 to July 2006, 403 patients were administered an anthracycline and/or a taxane as NC at the NCCH. Excluding the patients who received trastuzumab, the indication of which was not clear at the time of the study, concomitantly with a taxane, 368 patients who were diagnosed with breast cancer using pretreatment cutting needle biopsies were included in this study. The patient backgrounds are shown in Table 1. Among the patients, 194 (53%) were aged 50 years or younger and 174 (47%) were aged 51 years or older. The clinical stages of the patients at the first visit were IIA, IIB, IIIA, and IIIB for 29%, 31%, 13%, and 20%, respectively. According to the histological examinations of pretreatment cutting needle biopsies, 333 patients (90%) had an IDC, 19%, 36%, and 36% of which were classified as papillotubular type, solid-tubular type and scirrhous type, respectively. Other than IDC, 14 patients (4%) had an invasive lobular carcinoma (ILC) and 7 patients (2%) had a mucinous carcinoma.

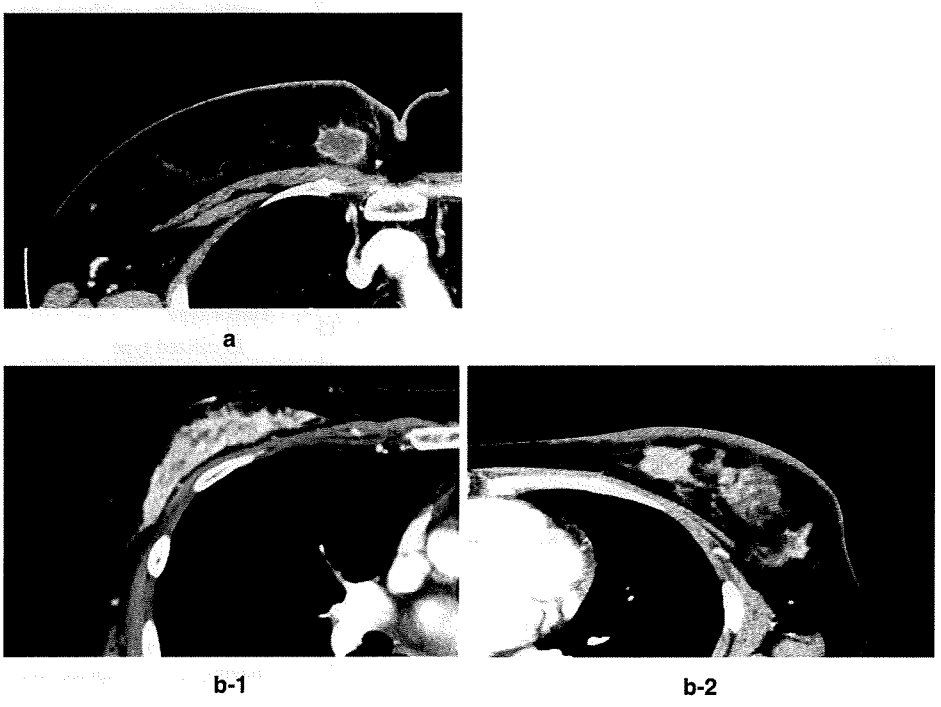

Fig. 1 Classification of tumor by CT imaging. **a** Localized type. **b-1** Nonlocalized type: glandular spreading. **b-2** Nonlocalized type: tumor with surrounding lesions

Table 1 Patient and disease characteristics ($N = 368$)

Parameter	No. of patients	%
Age (years)		
≤50	194	53
≥51	174	47
Clinical stage		
IIA	105	29
IIB	114	31
IIIA	74	13
IIIB	75	20
Pretreatment pathology		
Invasive ductal carcinoma	333	90
Papillotubular type	68	19
Solid-tubular type	131	36
Scirrhous type	134	36
Invasive lobular carcinoma	14	4
Mucinous carcinoma	7	2
Other	14	4
Hormone receptors		
ER positive	150	41
PgR positive	218	59
HER2		
Positive	57	15
Histological grade		
G1	18	5
G2	169	46
G3	181	49
Neoadjuvant chemotherapy		
AC	3	1
ACT	75	20
AT	185	50
FECT	92	25
T	13	4
Surgery		
Partial mastectomy	136	37
Total mastectomy	232	63
Clinical response		
CR	99	27
PR	218	59
NC	46	13
PD	5	1
Pathological response		
pCR	64	17
pINV	304	83
Postoperative pathological tumor size (mm)		
Median	24	
Range	0–130	
No. of pathological LN metastases		
0	164	45
1–3	108	29
4–9	58	16
≥10	38	10

PgR, progesterone receptor; *ER*, estrogen receptor; *CR*, complete response; *PR*, partial response; *NC*, neoadjuvant chemotherapy; *pCR*, pathological complete response; *LN*, lymph node

Immunohistological examinations revealed that 41%, 59%, and 15% of the patients were positive for ER, PgR, and HER-2, respectively. The histological grade was G2 and G3 in 46% and 49% of the patients, respectively, indicating that many patients had relatively high-grade disease. As NC regimens, AC, ACT, AT, FECT, and T were used in 1%, 20%, 50%, 25%, and 4% of the patients, respectively. The clinical response rate to NC was 86% (27% for cCR and 59% for cPR), and 64 patients (17%) achieved a pCR pathological response. The median postoperative pathological tumor size was 24 (range, 0–130) mm. Whereas 45% of the patients were node-negative, 16% of the patients had four or more and approximately 10% of the patients had ten or more metastatic lymph nodes. Among the 368 patients, we further examined 267 patients who underwent CT imaging before treatment (Table 2). Classification of the tumor shape based on CT imaging showed localized tumors in 65 patients (24%). The median maximum tumor size measured using pretreatment CT was 40 (range, 15–120) mm. When we compared pretreatment maximum tumor size and the postoperative pathological tumor size in these patients, the treatment reduced the maximum tumor size by 30% or more in 146 patients (55%).

Table 3 shows the results of univariate analysis performed to evaluate the relationship between the efficacy of

Table 2 Tumor characteristics in CT images ($N = 267$)

Parameter	No. of patients	%
Tumor type		
Localized type	65	24
Nonlocalized type	202	76
Pretreatment tumor size (mm)		
Median	40	
Range	15–120	
Tumor reduction rate[a]		
>30%	146	55
<30%	121	33

[a] x100 (Pretreatment tumor size − pathological tumor size)/pretreatment tumor size); pretreatment tumor sizes were measured in imaging from computed tomography

Table 3 Univariate analysis of predictive markers in pathological response and tumor reduction

Parameter	pCR		Tumor reduction rate >30%	
	n (%)	*p* value	*n* (%)	*p* value
Age (years)				
≥51	42[a] (22)	0.022	61 (52)	N.S.
≤50	22 (13)		85 (56)	
Invasive ductal carcinoma				
Solid-tubular type	35[a] (27)	0.0006	60[a] (67)	0.005
Scirrhous type	12[a] (8)	0.0006	50 (52)	N.S.
Papillotubular type	8 (12)	N.S.	29 (54)	N.S.
ER-negative	53[a] (24)	<0.0001	96 (59)	N.S.
ER-positive	11 (7)		50 (48)	
PgR-negative	50[a] (23)	0.0005	92 (58)	N.S.
PgR-positive	14 (9)		54 (50)	
HER2 3+	19[a] (33)	0.004	24 (55)	N.S.
HER2 2+	6 (11)		27 (66)	
HER2 <1+	39 (15)		95 (52)	
Histological grade G3	45[a] (25)	0.001	89[a] (70)	<0.0001
G2	17 (10)		49 (39)	
G1	2 (11)		7 (58)	
Clinical response				
CR + PR	62[a] (20)	0.0017	138[a] (60)	<0.0001
NC + PD	2 (3)		8 (22)	
CT tumor type				
Localized type	16 (24)	0.063	48[a] (74)	0.0003
Nonlocalized type	29 (14)		98 (49)	

[a] $p < 0.05$

CT, computed tomography; *ER*, estrogen receptor; *PgR*, progesterone receptor; *CR*, complete response; *PR*, partial response; *NC*, neoadjuvant chemotherapy

NC and the clinicopathological examination results. Significantly higher percentages of patients achieved pCR if they were aged 50 years or older, had solid-tubular type disease, were negative for ER or PgR, were positive for HER-2, had histological grade 3 disease, demonstrated positive clinical sensitivity (CR [complete response] + PR [partial response]), or were classified as having localized disease using pretreatment CT imaging. Conversely, significantly lower percentages of patients experienced pCR if their tumors were histologically classified as scirrhous. When the pretreatment maximum tumor size and the postoperative pathological maximum tumor size were compared, the clinicopathological factors that were significantly associated with 30% or more reductions in tumor size were having solid tubular-type disease, testing negative for ER, classification of histological grade 3, positive clinical sensitivity (CR + PR), and classification as localized tumors based on pretreatment CT imaging. Table 4 shows the results of multivariate analysis of these factors. In this analysis, the factor that was significantly associated with reduced rates of pCR was tumors classified as scirrhous. Other factors did not significantly influence the pathological response. Histological grade 3, positive clinical sensitivity (CR + PR), and classification as localized tumors were significantly associated with tumor size reduction.

Discussion

In recent years, NC has been used not only for locally advanced breast cancer but also for relatively early-stage breast cancer. This type of therapy is used to (1) achieve pCR; (2) enable breast conservation by reducing the size of the tumor; and (3) evaluate the sensitivity of the breast cancer to anticancer drugs.

The primary purpose of NC is to achieve pCR, which is based on the understanding that patients who experience pCR after NC have better prognoses relative to other patients [8]. To accomplish this purpose, it is necessary to characterize the cases of breast cancer that are more likely to achieve pCR and to select anticancer drugs that are appropriate for each case. Immunohistological examinations, including analyses of hormone receptors, HER-2 and

Table 4 Multivariate analysis

Parameter	pCR		Tumor reduction rate >30%	
	p value	Odds ratio	*p* value	Odds ratio
Age >51 years	NS		NS	
Solid-tubular type	NS		NS	
Scirrhous type	0.008	0.2 (−1.441 to −0.239)	NS	
ER-negative	NS		NS	
PgR-negative	NS		NS	
HER2 3+	NS		NS	
Histological grade G3	NS		<0.0001	3.76 (0.349–0.989)
CR + PR	NS		0.0003	5.28 (0.405–1.309)
Localized type	NS		0.012	2.42 (0.104–0.796)

CR, complete response; *PR*, partial response; *NS*, not significant

Ki-67, have been reported to relate to the efficacy of PST [9–12]. In our study, we examined the characteristics of breast cancer tumors that made it easier to achieve pCR with NC. In univariate analysis, histological grade 3 and solid-tubular type tumors as well as lack of ER and PgR overexpression and the presence of HER-2 overexpression were shown to be significantly associated with improved treatment efficacy. However, multivariate analysis revealed that cases classified as scirrhous type were significantly less likely to achieve pCR. Interestingly, PST has been reported to be less effective for ILC [13–15]. In this study ILC had few effect of tumor size reduction of NC and there was no pCR case in ILCs (data not shown). However, ILC was rare in Japan formerly and there were few ILC patients in this study. One of the reasons for this low efficacy may be that tumor cells from ILCs are relatively isolated and are distributed among the fibrous stroma, leading to less blood flow to the tumor and less drug accessibility. Scirrhous-type tumors, which were associated with less NC efficacy, are histologically similar to ILCs growing as the stroma grows with relatively isolated tumor cells. Therefore, these histological features may be related to the efficacy of NC for these tumors.

It has been reported that NC is useful for breast conservation after a reduction of tumor size [16–18]. In the EORTC10902 study, NC enabled breast conservation in 57 of 246 (23%) patients who were scheduled to undergo total mastectomies [16]. In the present study, we characterized the tumor sizes, which tended to be reduced by NC, using pretreatment CT imaging as well as clinicopathological examinations. Magnetic resonance imaging (MRI) is more widely used to plan adequate surgical treatment for early breast cancer than CT probably because of the risk of radiation exposure. However, CT scan has an important advantage compared with MRI because CT breast images are obtained in the supine position used during surgery, thus providing precise information about the tumor extent; in contrast, in most previous studies of MRI, patients were examined in the prone position to minimize motion of the breast during breathing. There are helical CT scanners in many medium and small Japanese hospitals. Therefore, we can use CT without circumstance. As a result, a significant reduction of tumor size was observed in cases classified as localized tumors, as well as those categorized as histological grade 3 disease and those that achieved CR or PR in terms of clinical efficacy. There are previous reports about NC reducing the sizes of tumors and the safety of breast-conserving therapy, including one from our institution [18–20]. When the tumors show sporadic shrinkage, they need to be resected carefully after NC because the remaining tumor cells can be diffusely distributed. In contrast, when the shrinkage pattern is concentric, NC is thought to be more effective for reducing the tumor size, making breast-conserving therapy safer. Therefore, localized tumors may achieve a favorable degree of reduction because they often shrink in a concentric manner. In evaluation of the tumor reduction rate, we classified the tumor shape, measured the pretreatment tumor size, and compared it with the post-operative pathological tumor size. The classification of tumors into localized or nonlocalized types using CT imaging provides a basis for making this determination. Localized tumors responded well to NC and were reduced into smaller, concentric tumors that could be safely treated by wide excision, giving a negative margin status. However, nonlocalized tumors diminished into a mosaic pattern of residual tumor cells, giving a positive margin status when treated with breast conserving therapy and tumor reduction rate were low. Multivariate analysis demonstrated that classification by CT was a powerful predictor of the tumor reduction rate by NC in this study. To the best of our knowledge, this is the first report to show that the tumor shape is useful as a predictive criterion for the efficacy of NC.

Breast cancer therapy with anticancer drugs is thought to result in equivalent survival rates when performed before or after surgery [8, 16]. Currently, both anthracyclines and taxanes are sufficiently used to increase the percentage of patients achieving pCR; however, there are no definitive criteria that detail the proper indications of various anticancer drugs for different types of tumors. Therefore, unnecessary drugs may be administered to patients in excessive doses. The postoperative adjuvant therapy for primary breast cancer is provided in accordance with the recommendations from the St. Gallen consensus meeting [21]. Although adjuvant chemotherapy is considered to be standard for node-positive patients, many aspects concerning the administration of anticancer drugs to node-negative patients have not been clarified. In particular, whether the anthracyclines and taxanes used for NC are necessary for these node-negative patients is not clear, and thus, these drugs may be used excessively for these patients. We believe that it is critical to predict the efficacy of drugs used for different purposes to determine which drugs and doses should be for each patient. In the NSABPB-27 study, the addition of a taxane to an anthracycline did not result in a significantly improved survival rate, which suggested that more specific criteria are needed to identify the cases in which taxanes produce an additive effect [1]. In recently published studies, the sensitivity of a certain drug was evaluated and then therapy was continued only for patients who experienced efficacy by adding the drug, whereas surgeries were performed for those who did not benefit from the medication. In fact, there are patients who do not benefit from widely used anticancer drugs, including anthracyclines and taxanes [21, 22]. Performing NC aggressively in these patients is disadvantageous. Thus,

it is important to identify tumors resistant to NC before the treatment and to exclude such cases from NC.

We have examined the predictability of NC efficacy, which has no current definitive indication. Regarding the prediction of efficacy to achieve pCR, high degrees of responsiveness is reportedly obtained with the concomitant use of trastuzumab in patients who have HER-2 overexpression [2]. At our institution, trastuzumab has been administered to these patients in recent years, leading to a markedly high pCR rate, which surpassed that achieved using NC with anthracyclines and taxanes. These patients, however, were not included in this study because we only recently started routinely using trastuzumab and many patients who showed HER-2 expression did not receive this agent early in the study. The examination of both pCR and tumor size reduction in the present study identified several factors that are useful to determine the indications of NC. This study indicated that pCR of scirrhous type for NC was difficult and the primary tumor with localized tumor type in CT imaging or histological grade 3 will be fairly reduced by NC. However, these features could not predict the response completely and terminate the NC premature in nonresponders. Additional cases and prospective studies that are focused on particular types of cases are necessary.

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生涯教育シリーズ——76

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相談支援センターの機能

Function of Cancer Care Support Center

若尾文彦
Fumihiko Wakao

設置の背景

がん患者・家族からのがん相談に対応する窓口を設置してほしいという要望に応える形で，2005年8月に厚生労働省がん対策推進本部が策定した「がん対策推進アクションプラン2005」[1]において，がん患者や地域医療機関からの相談対応を担う「相談支援センター」の設置を要件とする，がん診療拠点病院（仮称）の整備を推進することが盛り込まれた．このアクションプランを受けて，翌2006年2月1日に厚生労働省健康局長通知「がん診療連携拠点病院の整備について」が発出され，相談支援機能を有する部門を設置することが，がん診療連携拠点病院の指定を受けるための要件とされた．

相談支援センターとは

がん診療連携拠点病院の指定要件では，地域がん診療連携拠点病院内に相談支援機能を有する部門（相談支援センター等）を設置することに加え，①当該部門に専任者が1人以上配置されていること，②当該部門は，地域がん診療連携拠点病院内外の医療従事者の協力を得て，当該拠点病院内外の患者，家族および地域の医療機関等からの相談等に対応する体制を整備することとされた．

この②がポイントで，従来，病院内に設置された相談窓口は，その病院のスタッフがその病院にかかっている患者に対して相談を実施していたが，相談支援センターでは，「病院内外の医療従事者の協力を得て」「病院内外の患者等からの相談等に対応する」ことが求められている．

がん対策推進基本計画

2007年4～6月にがん患者・家族の代表を含むがん対策推進協議会で策定され，閣議決議を受けた「がん対策推進基本計画」[2]では，がん医療に関する相談支援および情報提供での取り組むべき施策として，「適切な指導助言を行うため，相談員を複数人以上専任で配置すること等が望まれる．その際には，相談支援に関し十分な経験を有する看護師等の医療従事者や患者団体等との連携について検討する」などとされ，個別目標として，「すべての相談支援センターにおいて，5年以内に，がん対策情報センターによる研修を修了した相談員を配置することを目標とする」とされた．

指定要件の更新

がん対策推進基本計画を受けて，2008年3月1日に厚生労働省健康局長通知「がん診療連携拠点病院の整備について」が発出され，相談支援センターの要件を含むがん診療連携拠点病院の指定要件が変更された．主な変更点は，相談員として，国立がんセンターがん対策情報センターによる研修を修了した専従および専任の相談支援に携わる者を，それぞれ1人以上配置すること，相談支援に関し十分な経験を有するがん患者団体との連携協力体制の構築に積極的に取り組むこと，などが追加された．また，相談支援センターの業務についても，若干の変更が加わり以下のようになった．

①がんの病態，標準的治療法等がん診療およびがんの予防・早期発見等に関する一

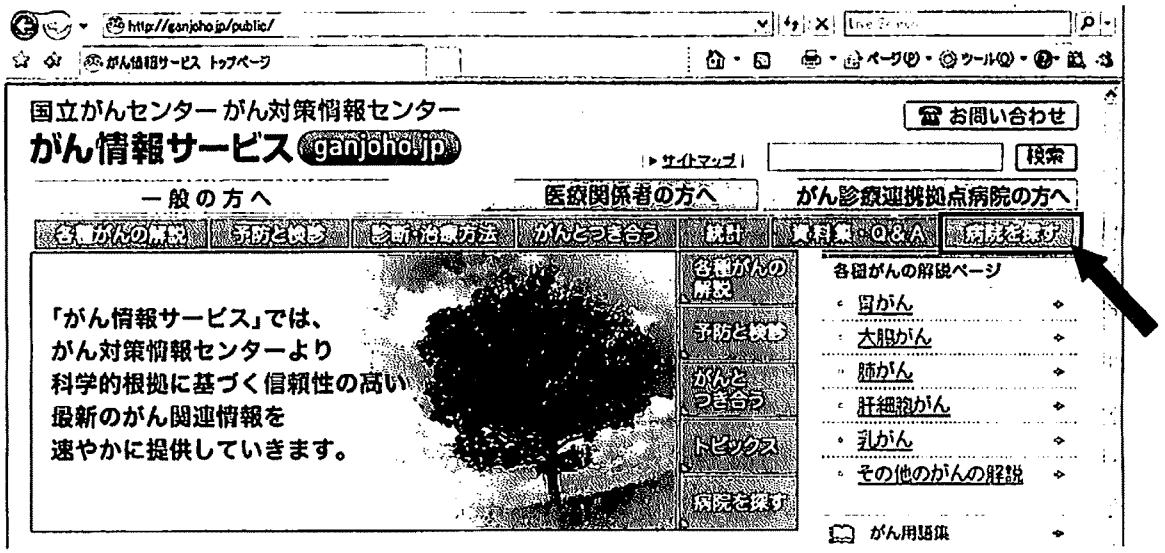

図1　がん情報サービス「一般の方へ」トップページ

般的な情報の提供

②診療機能，入院・外来の待ち時間および医療従事者の専門とする分野・経歴など，地域の医療機関および医療従事者に関する情報の収集，提供

③セカンドオピニオンの提示が可能な医師の紹介

④がん患者の療養上の相談

⑤地域の医療機関および医療従事者等におけるがん医療の連携協力体制の事例に関する情報の収集，提供

⑥アスベストによる肺がんおよび中皮腫に関する医療相談

⑦その他相談支援に関すること

相談員研修の実施

がん対策推進基本計画および，新指定要件を受けて，国立がんセンターがん対策情報センターでは，「相談支援センター相談員基礎研修会 (1)～(3)」と題して 2008 年末までに，計 7 回実施し，延べ 1,953 名が受講している．

相談支援センターの一覧

全国のがん診療連携拠点病院の一覧および相談センター一覧は，国立がんセンターがん対策情報センターのホームページ「がん情報サービス」に掲載されている．具体的には，がん情報サービス（http://ganjoho.jp）の「一般の方へ」のトップページ（図 1）の上部の右端にある「病院を探す」をクリックし，「がん診療連携拠点病院一覧」をクリックすると拠点病院一覧が，「相談支援センター一覧」をクリックすると相談支援センター一覧を参照することができ，このページにより，相談支援センターの名称，電話番号，担当者の職種などを参照することができる．

おわりに

相談支援センターは，いまだ発展途上であるが，研修が進み地域の協力体制が構築されれば，患者のみならず，医療従事者にとっても，重要ながんの情報基地になると考える．

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2) 厚生労働省健康局：「がん対策推進基本計画」の策定について．厚生労働省ホームページ，2007；http://www.mhlw.go.jp/shingi/2007/06/s0615-1.html

外来で診る食道がん・胃がん・大腸がん

総論

がん対策基本法とがん医療

Key Words

がん対策
がん医療
がん
医療政策

若尾文彦*

* 国立がんセンター
がん対策情報センター

がん対策基本法（図1）[1]

1. 成立の背景と基本理念

がんが国民の疾病による死亡の最大の原因となっている等がんが国民の生命および健康にとって重大な問題となっている．がん対策基本法は，その現状を踏まえて，がん対策の一層の充実を図るため，がん対策に関し，基本理念を定め，国，地方公共団体，医療保険者，国民および医師等の責務を明らかにし，並びにがん対策の推進に関する計画の策定について定めるとともに，がん対策の基本となる事項を定めることにより，がん対策を総合的かつ計画的に推進することを目的としたものである．2006年6月に成立し，2007年4月より施行されている．本法では，①がんの克服を目指し，がんに関する専門的，学際的または総合的な研究を推進するとともに，がんの予防，診断，治療等に係る技術の向上その他の研究等の成果を普及し，活用し，および発展させること，②がん患者がその居住する地域にかかわらず等しく科学的知見に基づく適切ながんに係る医療）を受けることができるようにすること，③がん患者の置かれている状況に応じ，本人の意向を十分尊重してがんの治療方法等が選択されるようがん医療を提供する体制の整備がなされること，の3つを基本理念としている．

2. 関係者の責務

がん対策基本法では，国，地方公共団体等，関係者の責務を謳っている．国は，基本理念にのっとり，がん対策を総合的に策定し，および実施する責務，地方公共団体は，基本理念にのっとり，がん対策に関し，国との連携を図りつつ，自主的かつ主体的に，その地域の特性に応じた施策を策定し，および実施する責務を有するとしている．また，医療保険者は，国および地方公共団体が講ずるがんの予防に関する啓発および知識の普及，がん検診に関する普及啓発等の施策に協力するよう努めなければならないとし，国民は，喫煙，食生活，運動その他の生活習慣が健康に及ぼす影響等がんに関する正しい知識を持ち，がんの予防に必要な注意を払うよう努めるとともに，必要に応じがん検診を受けるよう努めなければならないとしている．さらに，医師その他の医療関係者は，国および地方公共団体が講ずるがん対策に協力し，がんの予防に

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寄与するよう努めるとともに，がん患者の置かれている状況を深く認識し，良質かつ適切ながん医療を行うよう努めなければならないとしている．

3. 基本的施策

がん対策基本法で，がんの予防および早期発見の推進，がん医療の均てん化の促進等，研究の推進等の3つを基本的施策としてあげている．

がんの予防および早期発見の推進では，喫煙，食生活，運動その他の生活習慣および生活環境が健康に及ぼす影響に関する普及啓発，がんの予防の推進のために必要な施策と，がん検診の方法等の検討，がん検診の事業評価の実施，がん検診に携わる医療従事者に対する研修の機会の確保などその他のがん検診の質の向上等を図るために必要な施策を講ずる．さらに，がん検診の受診率の向上に資するよう，がん検診に関する普及啓発その他の必要な施策を講ずるものとしている．

がん医療の均てん化の促進等では，がん医療に携わる専門的な知識および技能を有する医師その他の医療従事者の育成を図るために必要な施策，がん患者がその居住する地域にかかわらず等しくそのがんの状態に応じた適切ながん医療を受けることができるよう，専門的ながん医療の提供等を行う医療機関の整備を図るために必要な施策，がん患者に対し適切ながん医療が提供されるよう，国立がんセンター，専門的ながん医療を提供する医療機関，その他の医療機関等の間における連携協力体制の整備を図るために必要な施策を講じるとされている．また，がん患者の状況に応じて疼痛等の緩和を目的とする医療が早期から適切に行われるようにすること，居宅においてがん患者に対しがん医療を提供するための連携協力体制を確保すること，医療従事者に対するがん患者の療養生活の質の維持向

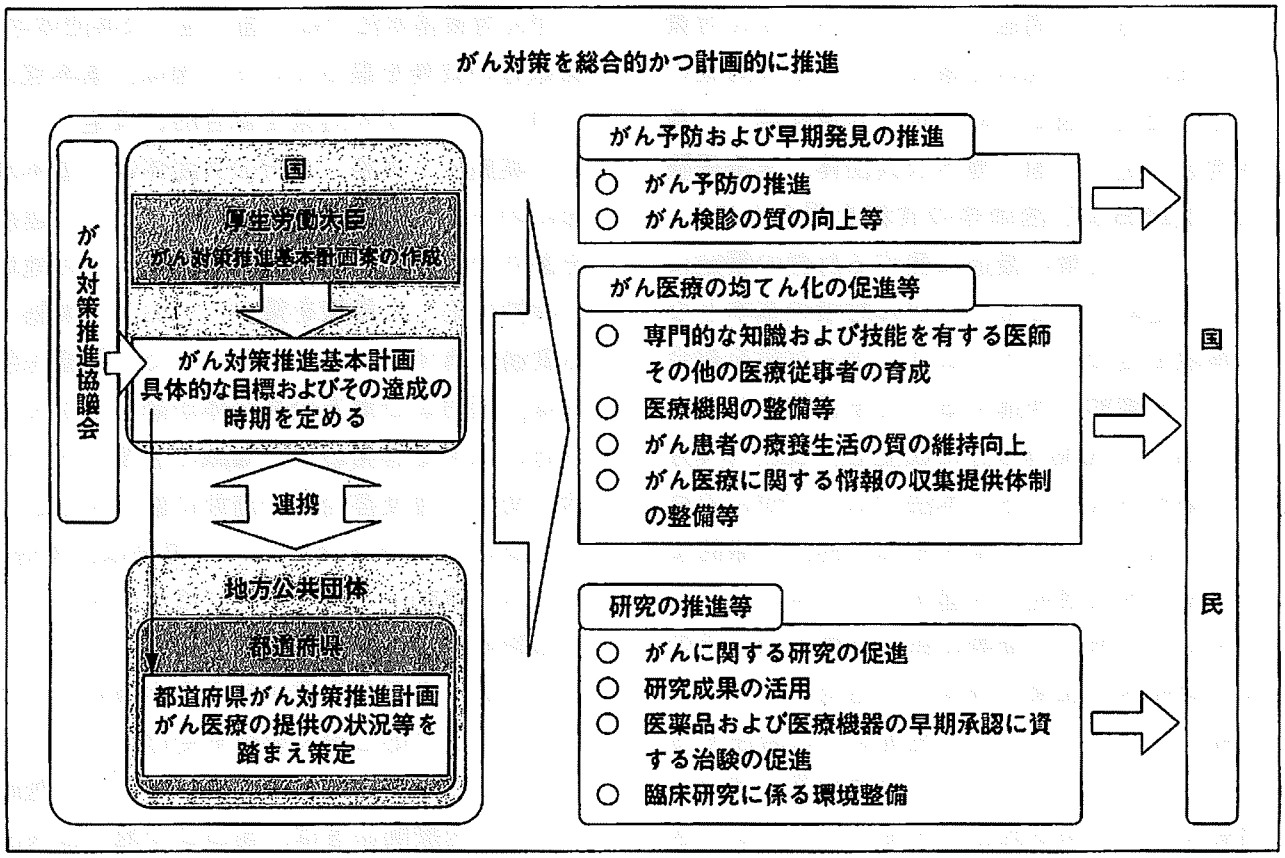

図1 がん対策基本法（2007年4月施行）

上に関する研修の機会を確保すること等がん患者の療養生活の質の維持向上のために必要な施策を講じるとしている．さらに，がん医療に関する情報の収集および提供を行う体制を整備するために必要な施策を講ずるとともに，がん患者およびその家族に対する相談支援等を推進するために必要な施策，がん患者のがんの罹り患，転帰その他の状況を把握し，分析するための取組を支援するために必要な施策を講ずるものとしている．

研究の推進等では，がんに関する研究の促進，研究成果の活用，医薬品および医療機器の早期承認に資する治験の促進，臨床研究に係る環境整備等をあげ，がんの本態解明，革新的ながんの予防，診断及び治療に関する方法の開発その他のがんの罹患率およびがんによる死亡率の低下に資する事項についての研究が促進され，並びにその成果が活用されるよう必要な施策，がん医療を行う上で特に必要性が高い医薬品および医療機器の早期の薬事法の規定による製造販売の承認に資するようその治験が迅速かつ確実に行われ，並びにがん医療に係る標準的な治療方法の開発に係る臨床研究が円滑に行われる環境の整備のために必要な施策を講ずるものとしている．

がん対策推進基本計画（図2）[2)]

2007年4月，がん対策基本法が施行され，基本法に基づいて，患者・家族の代表を含むがん対策推進協議会が召集され，4月・5月に6回の集中審議を行い，がん対策推進基本計画（案）が作成され，2007年6月15日に閣議決議された．がん対策推進基本計画は，長期的視点に立ちつつ，2007年度～2011年度までの5年間を対象として，がん対策の総合的かつ計画的な推進を図るため，がん対策の基本的方向について定めるとともに，都道府県がん対策推進計画（以下「都道府県計画」とい

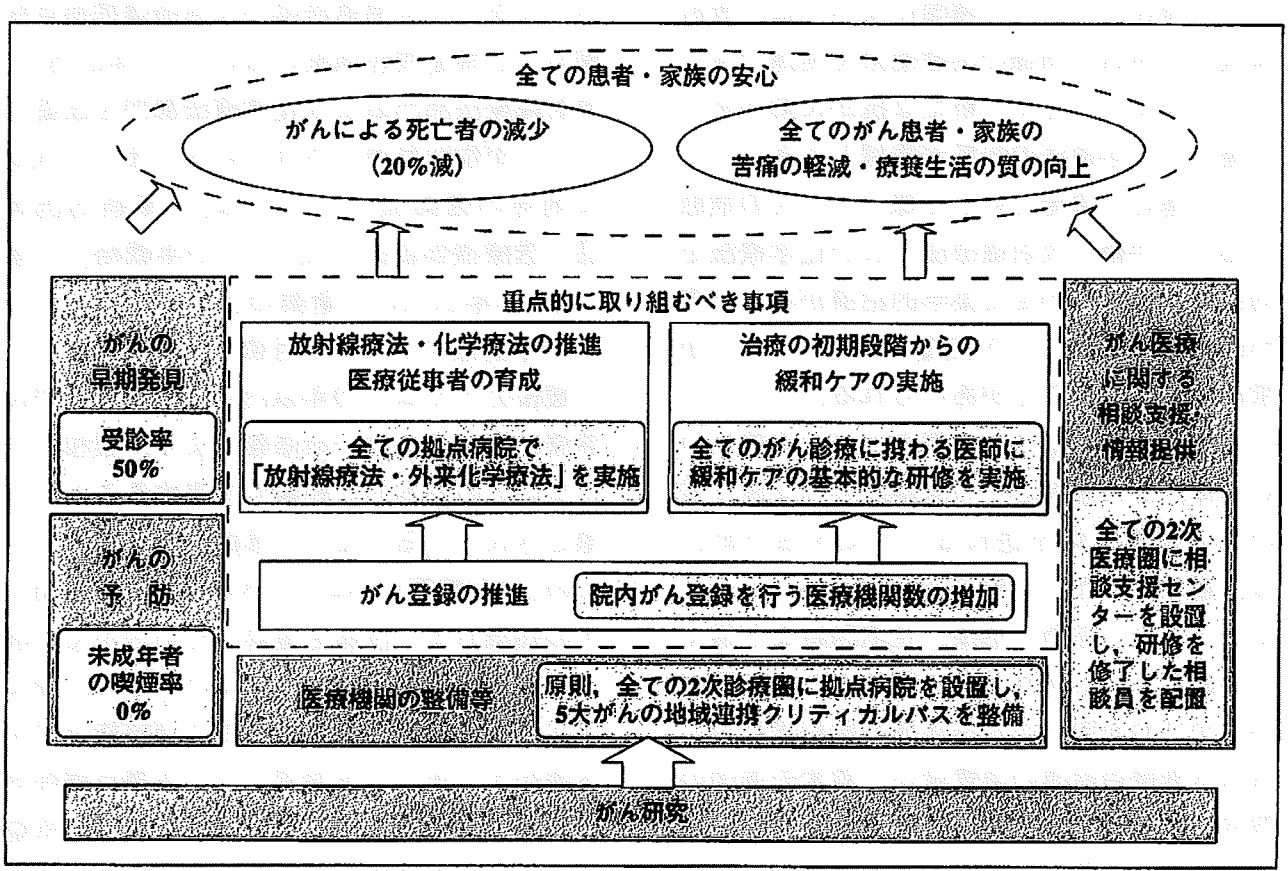

図2 がん対策推進基本計画

う）の基本となるものとされている．

1．重点的に取組むべき課題

基本方針として，がん患者を含めた国民の視点に立ったがん対策の実施，重点的に取り組むべき課題を定めた総合的かつ計画的ながん対策の実施をあげ，重点的に取り組むべき課題として，放射線療法および化学療法の推進並びにこれらを専門的に行う医師等の育成，治療の初期段階からの緩和ケアの実施，がん登録の推進をあげている．全体目標としては，がんによる死亡者の減少とすべてのがん患者およびその家族の苦痛の軽減並びに療養生活の質の維持向上があげられている．

放射線療法および化学療法の推進並びにこれらを専門的に行う医師の育成が重点課題となった背景として，わが国においては，胃がんなど，主として手術に適したがんが多かったこともあり，手術を行う医師が，化学療法も実施するなど，がん治療の中心を担ってきたが，現在は，がんの種類によっては，放射線療法が手術と同様の治療効果を発揮できるようになるとともに，新たな抗がん剤が多く登場し，化学療法の知見が蓄積してきたことから，進行・再発といった様々ながんの病態に応じ，手術，放射線療法および化学療法を効果的に組み合わせた集学的治療が各々を専門的に行う医師により実施されていくことが求められていることがあげられる．

治療の初期段階からの緩和ケアの実施については，がん患者とその家族が可能な限り質の高い療養生活を送れるようにするためには，緩和ケアが，治療の初期段階から行われるとともに，診断，治療，在宅医療など様々な場面において切れ目なく実施される必要があるが，わが国のがん性疼痛の緩和等に用いられる医療用麻薬の消費量が，欧米先進国の数分の一程度にとどまっていることや，がん診療に携わる医師の緩和ケアの重要性に対する認識が不十分であること等の改善が求められていることがあげられる．

2．分野別施策およびその成果や達成度を計るための個別目標

分野別施策として，(1) がん医療，(2) 医療機関の整備等，(3) がん医療に関する相談支援および情報提供，(4) がん登録，(5) がんの予防，(6) がんの早期発見，(7) がん研究，があげられる．(1) がん医療では，①放射線療法および化学療法の推進並びに医療従事者の育成，②緩和ケア，③在宅医療，④診療ガイドラインの作成，⑤その他が小項目としてあげられている．

放射線療法および化学療法の推進並びに医療従事者の育成では，がん診療を行っている医療機関が放射線療法および化学療法を実施できるようにするため，まずはその先導役として，すべての拠点病院において，5年以内に，放射線療法および外来化学療法を実施できる体制を整備するとともに，拠点病院のうち，少なくとも都道府県がん診療連携拠点病院および特定機能病院において，5年以内に，放射線療法部門および化学療法部門を設置することが個別目標とされている．また，抗がん剤等の医薬品については，「革新的医薬品・医療機器創出のための5か年戦略」に基づき，5年以内に，新薬の上市までの期間を2．5年短縮することが目標とされている．

緩和ケアでは，10年以内に，すべてのがん診療に携わる医師が研修等により，緩和ケアについての基本的な知識を習得することが目標とされている．また，原則として全国すべての2次医療圏において，5年以内に，緩和ケアの知識および技能を習得しているがん診療に携わる医師数を増加させるとともに，緩和ケアに関する専門的な知識および技能を有する緩和ケアチームを設置している拠点病院等がん診療を行っている医療機関を複数箇所整備することが目標とされている．

診療ガイドラインでは，科学的根拠に基づ

いて作成可能なすべてのがんの種類についての診療ガイドラインを作成するとともに，必要に応じて更新していくことが目標とされている．

医療機関の整備等では，原則として全国すべての2次医療圏において，3年以内に，概ね1か所程度拠点病院を整備するとともに，すべての拠点病院において，5年以内に，5大がん（肺がん，胃がん，肝がん，大腸がん，乳がん）に関する地域連携クリティカルパスを整備することが目標とされている．

がん医療に関する相談支援及び情報提供では，原則として全国すべての2次医療圏において，3年以内に，相談支援センターを概ね1か所程度整備するとともに，すべての相談支援センターにおいて，5年以内に，がん対策情報センターによる研修を修了した相談員を配置することが目標とされている．また，がんに関する情報を掲載したパンフレットの種類を増加させるとともに，当該パンフレットを配布する医療機関等の数を増加させることが目標とされ，加えて，当該パンフレットや，がんの種類による特性等も踏まえた患者必携等に含まれる情報をすべてのがん患者およびその家族が入手できるようにすることが目標とされている．さらに，拠点病院における診療実績，専門的にがん診療を行う医師および臨床試験の実施状況に関する情報等をさらに充実させることも目標されている．

がん登録では，院内がん登録を実施している医療機関数を増加させるとともに，すべての拠点病院における院内がん登録の実施状況を把握し，その状況を改善することが目標とされている．また，すべての拠点病院において，5年以内に，がん登録の実務を担う者が必要な研修を受講すること，がん登録に対する国民の認知度調査を行うとともに，がん登録の在り方についてさらなる検討を行い，その課題および対応策を取りまとめることが目標とされている．

がんの予防では，発がんリスクの低減を図るため，たばこ対策について，すべての国民が喫煙の及ぼす健康影響について十分に認識すること，適切な受動喫煙防止対策を実施すること，未成年者の喫煙率を3年以内に0%とすること，さらに，禁煙支援プログラムのさらなる普及を図りつつ，喫煙をやめたい人に対する禁煙支援を行っていくことが目標とされている．また，健康日本21に掲げられている「野菜の摂取量の増加」，「1日の食事において，果物類を摂取している者の増加」および「脂肪エネルギー比率の減少」等も目標とされている．

がんの早期発見では，がん検診の受診率について，欧米諸国に比べて低いことも踏まえ，効果的・効率的な受診間隔や重点的に受診勧奨すべき対象者を考慮しつつ，5年以内に50%以上（乳がん検診，大腸がん検診等）とすることが目標とされている．また，すべての市町村において，精度管理・事業評価が実施されるとともに，科学的根拠に基づくがん検診が実施されることが目標とされている．

がん研究では，がんによる死亡者の減少，すべてのがん患者およびその家族の苦痛の軽減並びに療養生活の質の維持向上を実現するためのがん対策に資する研究をより一層推進していくことが目標とされている．

3. がん対策を総合的かつ計画的に推進するために必要な事項

がん対策を総合的かつ計画的に推進するために必要な事項として，①関係者等の有機的連携・協力のさらなる強化，②都道府県による都道府県計画の策定，③関係者等の意見の把握，④がん患者を含めた国民等の努力，⑤必要な財政措置の実施および予算の効率化・重点化，⑥目標の達成状況の把握および効果に関する評価，⑦基本計画の見直し，があげられている．この中のがん患者を含めた国民

等の努力として，(a) がん患者およびその家族は，がん医療が医療従事者とのよりよい人間関係を基盤として成り立っていることを踏まえ，相互に信頼関係を構築することができるように努めること，(b) がん患者およびその家族は，医療従事者と協力して治療を進め，治療内容について医療従事者と共有できるようにすること，(c) がん患者および患者団体等は，がん対策において担うべき役割として医療政策決定の場に参加し，行政機関や医療従事者と協力しつつがん医療を変えるとの責任や自覚を持って活動していくこと，があげられている．

おわりに

以上のように，がん対策基本法の成立により，患者の視点に立ったがん対策推進基本計画が策定され，全国に375か所のがん診療連携拠点病院が指定され，さらに，各都道府県でがん対策推進計画が策定され，様々な取組が実施されているところである．このように，基本法によって，がんの医療が変わりつつあると思われ，「基本計画に基づき，国及び地方公共団体，また，がん患者を含めた国民，医療従事者，医療保険者，学会，患者団体を含めた関係団体及びマスメディア等が一体となってがん対策に取り組み，がん患者を含めた国民が，進行・再発といった様々ながんの病態に応じて，安心・納得できるがん医療を受けられるようにするなど，『がん患者を含めた国民が，がんを知り，がんと向き合い，がんに負けることのない社会」の実現を目指して行く』」ことが求められていると考える．

文　献

1) がん対策基本法：
http://www.mhlw.go.jp/shingi/2007/04/dl/s0405-3a.pdf
2) がん対策推進基本計画：
http://www.mhlw.go.jp/shingi/2007/06/s0615-1.html

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Characteristics and outcomes of patients with advanced non-small-cell lung cancer who declined to participate in randomised clinical chemotherapy trials

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There are inadequate data on the outcomes of patients who declined to participate in randomised clinical trials as compared with those of participants. We retrospectively reviewed the patient characteristics and treatment outcomes of both participants and non-participants in the two randomised trials for chemotherapy-naive advanced non-small-cell lung cancer. Trial 1 compared four platinum-based combination regimens. Trial 2 compared two sequences of carboplatin plus paclitaxel and gefitinib therapies. Nineteen of 119 (16%) and 153 (37%) patients declined to participate in Trials 1 and 2, respectively. Among the background patient characteristics, the only variable associated with trial participation or declining was the patients' attending physicians ($P<0.001$). Important differences were not observed in the clinical outcomes between participants and non-participants, for whom the response rates were 30.6 *vs* 34.2% and the median survival times were 489 *vs* 461 days, respectively. The hazard ratio for overall survival, adjusted for other confounding variables, was 0.965 (95% confidence interval: 0.73–1.28). In conclusion, there was no evidence to suggest any difference in the characteristics and clinical outcomes between participants and non-participants. Trial designs and the doctor–patient relationship may have an impact on the patient accrual to randomised trials.
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Randomised clinical trials (RCTs) are the definitive method for comparing the efficacy of treatments and a crucial step in the development of new cancer treatments. There has always been a big problem that their low accrual rates limit their progress (Lara *et al*, 2001; Corrie *et al*, 2003; Go *et al*, 2006).

A number of studies have examined the motivations of patients for accepting or declining entry to RCTs (Jenkins and Fallowfield, 2000; Madsen *et al*, 2000, 2002; Ellis *et al*, 2001; Wright *et al*, 2004; Ho *et al*, 2006; Albrecht *et al*, 2008). The results of questionnaire surveys administered to patients regarding clinical trials revealed that two of the most common reasons for entering the trial were the hope for personal benefit and the opportunity to contribute to the research knowledge thereby benefiting others in the future (Jenkins and Fallowfield, 2000; Madsen *et al*, 2000, 2002; Ellis *et al*, 2001; Wright *et al*, 2004; Albrecht *et al*, 2008). On the other hand, the common reasons for declining participation were worries about the process of randomisation, overestimation of the benefits of standard therapy and fear of the trial's experimental nature (Jenkins and Fallowfield, 2000; Ellis *et al*, 2001; Ho *et al*, 2006).

However, inadequate data are available on the actual outcomes of non-participants compared with those participating in RCTs (Schmoor *et al*, 1996; Braunholtz *et al*, 2001; Burgers *et al*, 2002; Peppercorn *et al*, 2004; West *et al*, 2005). Although several reports and their review (Braunholtz *et al*, 2001) have suggested the existence of a 'trial effect', in which participants enjoy favourable outcomes, others, especially those which attempted to exclude the confounding factors, have refuted this finding (Schmoor *et al*, 1996; Burgers *et al*, 2002; Peppercorn *et al*, 2004; West *et al*, 2005).

On the other hand, if participation in prospective trials is associated with certain clinical characteristics of the patients, generalisability of the conclusion from the data to the clinical practise, even in patients who meet the restrictive eligibility criteria, should be in question.

The purpose of this study was to analyse the characteristics and outcomes of the patients who met the eligibility criteria but declined to participate in RCTs, as compared with those who did participate, and to search for clues to improve patient accrual to clinical trials.

MATERIALS AND METHODS

Between October 2000 and October 2005, each of the 272 patients, who fulfilled the entry criteria of our top priority studies during the period, was informed of all aspects of RCTs on non-small-cell lung cancer (NSCLC) and was invited to participate in one of the two trials to be conducted at the National Cancer Center Hospital, Tokyo, Japan. We make it a rule for each patient with advanced

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lung cancer to be hospitalised for the first-line chemotherapy. All patients are then checked for the eligibility criteria of clinical trials available at the time and recorded in our database, whether or not they are treated on trials.

Signed informed consent was obtained from the patients for future statistical analysis of their clinical courses and outcomes, even when they were treated outside clinical trials.

Trial 1 was conducted to compare the four platinum-based combination regimens (cisplatin–irinotecan, carboplatin–paclitaxel, cisplatin–gemcitabine and cisplatin–vinorelbine) in patients with untreated advanced NSCLC between October 2000 and June 2002 (Ohe *et al*, 2007). When patients declined to participate, cisplatin-based combination regimens, such as cisplatin–irinotecan, the reference arm of the trial, were recommended. The patients ultimately selected the treatment following discussions with their families and the physicians.

Trial 2 was conducted between June 2003 and October 2005 to compare the following two treatment arms; (A) four courses of carboplatin and paclitaxel (CP) followed by gefitinib, and (B) gefitinib until disease progression followed by CP, in patients with advanced NSCLC (Nokihara *et al*, 2008). When patients declined to participate, platinum-based combination regimens, such as CP, were recommended. The patients ultimately selected the treatment following discussions with their families and the physicians; treatment options included gefitinib as first-line chemotherapy, when the patients and their families wished to start with it.

Patients in each trial had to meet the following criteria: histologically and/or cytologically documented NSCLC; clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy); no earlier systematic chemotherapy; at least one measurable lesion; age 20–74 years old; Eastern Cooperative Oncology Group Performance Status (PS) of 0 or 1; adequate haematological, hepatic and renal functions; and partial pressure of arterial oxygen of 60 torr or more. Each patient was required to submit a written informed consent before entry.

Four physicians (A, B, C and D) participated in Trial 1 and five physicians (A, B, C, D and E) in Trial 2. All were male. Physicians A, B, C and D had 16, 14, 11 and 9 years of experience, respectively, at the time of activation of Trial 1 (October 2000), and Physician E had 9 years of experience at the start of Trial 2 (June 2003). One of the five attending staff physicians and one to two residents or trainees attended each consultation. Which doctor actually offered the RCTs depended on each case and was not recorded, but the attending staff physician finally confirmed the decision by the patient.

Paper and/or electronic medical records from the initial visit to our centre to the end of the follow-up were retrospectively reviewed. Demographic data (age, gender, smoking history), medical information (tumour histology, clinical stage, performance status, therapy characteristics), and clinical outcomes (response rate, follow-up time, overall survival time, 1- and 2-year survival rates) were abstracted and analysed. The response was evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST) (Therasse *et al*, 2000) by the attending physicians. It is our policy to assess clinical responses with RECIST, even in routine practise. Follow-up time at our institution was defined as the period from the initiation of the first day of the initial therapy or decision of no therapy, to the last day at our institution (including death during follow-up). Survival data of the patients who left our institution could be collected by enquiry into official agency for family registry in Japan.

χ^2-tests and logistic regression analysis was used to assess associations between patient characteristics and the rate of declining to participate. Overall survival (OS) curves were produced using the Kaplan–Meier method and compared with the log rank test. All participants (those who agreed to be enroled into the RCT) and non-participants (those who declined to participate in the RCT) were included in the OS analysis. A Cox proportional hazards model was used to adjust for other potential confounding factors (age, gender, smoking history, clinical stage and PS) in comparing the OS of participants and non-participants. *P*-values <0.05 were considered statistically significant. The data collected were analysed using an SPSS II statistical package.

Japanese ethics guidelines for clinical and epidemiological studies, which took effect in August 2007, do not mandate institutional review board (IRB) approval for a single-institutional, retrospective data analysis from the medical charts, when the predesignated person of the institution so judges. This study was thus exempted from ethical review of IRB in due process, on the judgment of the responsible official, deputy director of National Cancer Center Hospital.

RESULTS

There were no significant differences in the outcomes between the arms of each trial. In Trial 1, no statistically significant differences in the response rate, progression-free survival and OS were observed between the four regimens. In Trial 2, there were no statistically significant differences in the median survival time (MST) (18.8 and 17.2 months) and the survival rate at 1 year between the two arms. Seventy-five patients declined to participate in those trials, and 1 of the 197 who initially accepted entry withdrew consent, refusing to continue the trial immediately after randomisation.

Table 1 shows the patient characteristics and rate of declining. 100 patients accepted and 19 patients (16%) declined entry to Trial 1, and 96 patients accepted and 57 patients (37%) declined entry to clinical Trial 2 (including the one patient already mentioned who withdrew consent after randomisation) ($P<0.001$). No significant influence on the rate of declining of patient gender, age,

Table 1 Patient characteristics and rate of declining

	Clinical trial 1			Clinical trial 2			Total		
	P	NP	ROD (%)	P	NP	ROD (%)	P	NP	ROD (%)
No.	100	19	16	96	57	37	196	76	28
Gender									
Male	64	12	16	55	34	38	119	46	28
Female	36	7	16	41	23	36	77	30	28
Age									
<60	46	9	16	37	29	44	83	38	31
⩾60	54	10	16	59	28	32	113	38	25
Smoking history									
+	69	9	12	55	33	38	124	43	26
–	31	10	24	41	24	37	72	33	31
Clinical stage									
III	24	6	20	21	19	48	45	25	36
IV	76	13	15	75	38	34	151	51	25
PS									
0	27	4	13	47	19	29	74	23	24
1	73	15	17	49	38	44	122	53	30
Physicians									
A	32	5	14	23	25	52	55	30	35
B	28	0	0	25	1	4	53	1	2
C	18	2	10	34	4	11	52	6	10
D	22	12	35	7	18	72	29	30	51
E	—	—	—	7	9	56	7	9	56

Abbreviations: NP = non-participants, P = participants; PS = performance status; ROD = rate of declining.

Table 2 Prediction of participation or declining to trials

	Univariate analysis[a]		Multivariate analysis[b]	
	Odds ratio (95% CI)	***P*-value**	**Odds ratio (95% CI)**	***P*-value**
Gender (male *vs* female)	1.008 (0.586–1.733)	0.977	0.646 (0.300–1.391)	0.264
Age (<60 *vs* ⩾60)	0.735 (0.432–1.250)	0.254	0.701 (0.376–1.310)	0.266
Smoking history (+ *vs* −)	1.394 (0.815–2.386)	0.225	2.538 (1.162–5.541)	0.019
Clinical stage (III *vs* IV)	0.608 (0.339–1.089)	0.093	0.681 (0.346–1.340)	0.266
PS (0 *vs* 1)	1.398 (0.792–2.467)	0.247	0.785 (0.396–1.554)	0.487
Physicians (A–E)		<0.001		<0.001

Abbreviations: NP = non-participant; P = participant; PS = performance status; ROD = rate of declining. [a]By Pearson's χ^2-test. [b]By logistic regression analysis.

Table 3 Number of courses of the first-line chemotherapy

	Clinical trial 1		Clinical trial 2		
	Participants	**Non-participants**	**Participants**	**Non-participants**	***P*-value**
	100	16	96	57	
First-line cycles					
1	10 (10%)	4 (25%)	6 (12%)	4 (9%)	0.418[a]
2	18 (18%)	4 (25%)	8 (16%)	12 (27%)	
3	37 (37%)	7 (44%)	5 (10%)	9 (20%)	
⩾4	35 (35%)	1 (6%)	30 (61%)	20 (44%)	
Gefitinib median duration (day)			73	99	0.118[b]
Range			13–752	34–1065	
IQR			29–204	38.5–512	

Abbreviation: IQR = interquartile range. [a]By Pearson's χ^2-test. [b]By log rank test.

smoking history, tumour histology, clinical stage or PS was observed (Table 2). There were, however, large differences in the rates of decline among the attending physicians who informed the patients about the trials and asked them to participate ($P<0.001$).

The treatment regimens for those who declined participation in the clinical trials were as follows. The majority of those who declined participation in Trial 1 selected one of the four platinum-based combination regimens presented in the trial: cisplatin–irinotecan 4, cisplatin–vinorelbine 3, cisplatin–gemcitabine 1, carboplatin–paclitaxel 4. Three patients in Trial 1 desired to have no more active treatments and opted for supportive care only, but later received active treatment at their referred hospitals. The detail of their therapy is unknown.

The majority of those who declined participation in Trial 2 selected carboplatin-based combination chemotherapy: carboplatin–paclitaxel 34 and carboplatin–gemcitabine 11, there by reflecting the shift to carboplatin for advanced NSCLC in Japan at the time of Trial 2, on the basis of the reports on the activity of the carboplatin-based regimens (Kelly *et al*, 2001; Schiller *et al*, 2002; Ohe *et al*, 2007). Twelve patients (21%) selected gefitinib as first-line chemotherapy.

Survival was analysed for all of the 196 participants and 76 of the non-participants. Post-therapy was analysed for all of the 196 participants and 73 of the non-participants, who were treated at our centre. There was one possible treatment-related death due to perforation of the colon during gefitinib treatment in Trial 2. No other toxic deaths were observed among either participants or non-participants. More participants of both the clinical trials were given four cycles or more of the first-line chemotherapy, probably reflecting protocol regulations (Table 3).

Table 4 summarises the treatment after the initial therapy. There were no significant differences between participants and non-participants in the number of chemotherapy regimens. Six (8%) of those who declined participation in the trial later participated in early-phase clinical trials of experimental therapies.

Table 4 Treatment after the first-line chemotherapy

	Participants 196 (%)	**Non-participants 73 (%)**	***P*-value[a]**
Chemotherapy regimen			
0[b]	26	40	0.108
1	38	26	
2	22	25	
3	9	8	
>4	5	1	
Radiotherapy	49	34	0.031
Pleural or pericardial drainage	10	5	0.227
Operation on metastatic brain tumors	1	3	0.122
Early-phase trials	13	8	0.300

[a]By Pearson's χ^2-test. [b]Patients received first-line chemotherapy only.

We have observed no clinically relevant differences in the clinical outcomes between participants and non-participants (Table 5). Clinical response to the initial therapy was analysed for all of the 196 participants and 73 of the non-participants, excluding three patients who were not treated at our institute. The response rate was 30.6% in participants and 34.2% in non-participants ($P=0.325$). The median follow-up time at our centre was 388 days for participants and 406 days for non-participants, which was not statistically different.

The OS was not different between participants and non-participants (Table 5 and Figure 1), with a hazard ratio of participants *vs* non-participants of 0.998 (95% confidence interval: 0.76–1.32). No significant difference in OS was observed either in Trial 1 (Figure 2) or in Trial 2 (Figure 3).

Table 5 Clinical outcomes

	Clinical trial 1		Clinical trial 2		Total		
	Participants	**Non-participants**	**Participants**	**Non-participants**	**Participants**	**Non-participants**	***P*-value**
Response rate (%)[a]	29 (29/100)	12.5 (2/16)	32.3 (31/96)	40 (23/57)	30.6 (60/196)	34.2 (25/73)	0.569[b]
Median follow-up time (day)	329	339	493	444	388	406	0.846[c]
Range	45–2704	1–2176	36–2036	22–1688	36–2704	1–2176	
IQR	177–665	59–582	213–861	175–658	197–742	146–604	
Median survival time (day)	416	408	573	519	489	461	0.987[c]
Range	34–2704	53–2380	40–2036	35–1688	34–2704	35–2380	
IQR	264–815	140–698	251–938	276–1012	259–863	229–774	
1-year survival (%)	56.0	63.2	65.6	64.9	60.7	64.5	0.567[b]
2-year survival (%)	29.4	21.1	38.5	29.8	33.9	27.6	0.379[b]

Abbreviation: IQR = interquartile range. [a]Excluding three patients who did not receive active treatment at our center. [b]By Pearson's χ^2-test. [c]By log rank test.

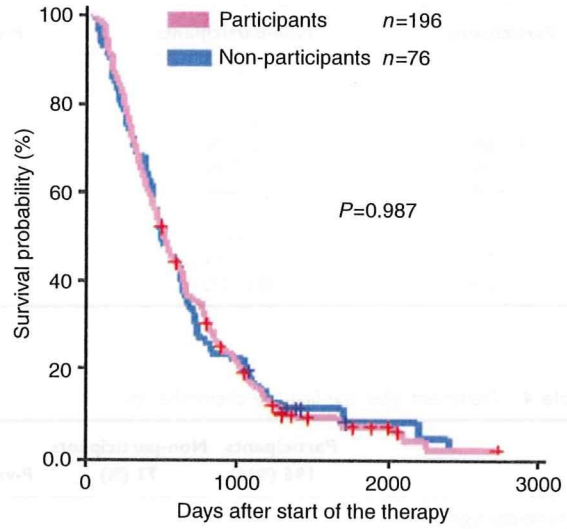

Figure 1 Overall survival of those who declined to participate in randomised trials (blue line, $n = 76$) as compared with the participants (pink line, $n = 196$). No significant difference can be observed.

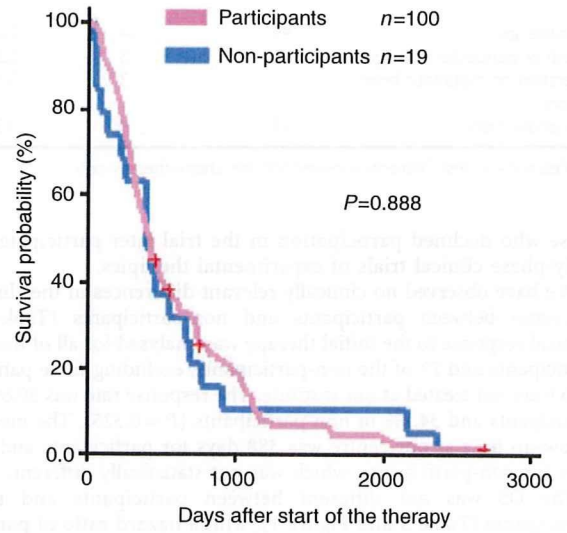

Figure 2 Overall survival of those who declined to participate in Trial 1 (blue line, $n = 19$) as compared with the participants (pink line, $n = 100$). No significant difference can be observed.

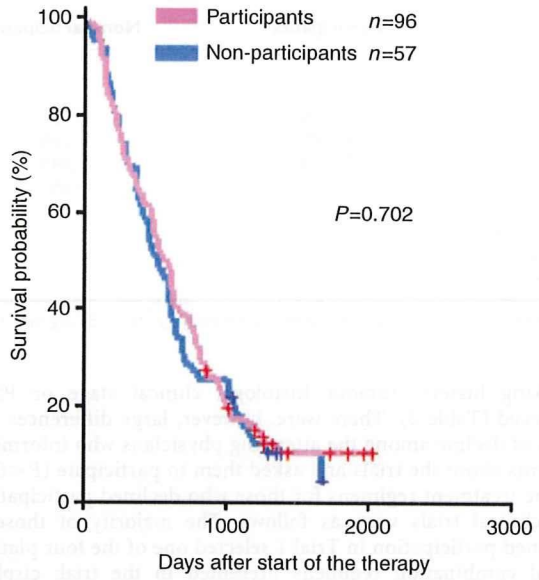

Figure 3 Overall survival of those who declined to participate in Trial 2 (blue line, $n = 57$) as compared with the participants (pink line, $n = 96$). No significant difference can be observed.

With the Cox proportional hazards model adjusted for gender, age, smoking history, clinical stage and PS, the hazard ratio of participants *vs* non-participants was 0.965 (95% confidence interval: 0.73–1.28, $P = 0.805$). Among the patient characteristics, PS was the only significant factor associated with OS in multivariate analysis ($P = 0.006$, by Cox proportional model).

DISCUSSION

It has been argued that trial participants have better outcomes than those who are not enroled in clinical trials. Several investigations have reported a favourable overall trend with trial entry (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004; West *et al*, 2005). This 'trial effect' could derive from several factors, such as protocol effect (the way treatments are delivered), care effect (extra care related to data gathering), Hawthorne effect (changes in doctor or patient behaviour on the basis of the knowledge that they are under observation) or placebo effect (psychologically mediated benefits) (Braunholtz *et al*, 2001; Peppercorn *et al*, 2004).

In majority of the reports comparing outcomes between participants and non-participants of clinical trials, however, the