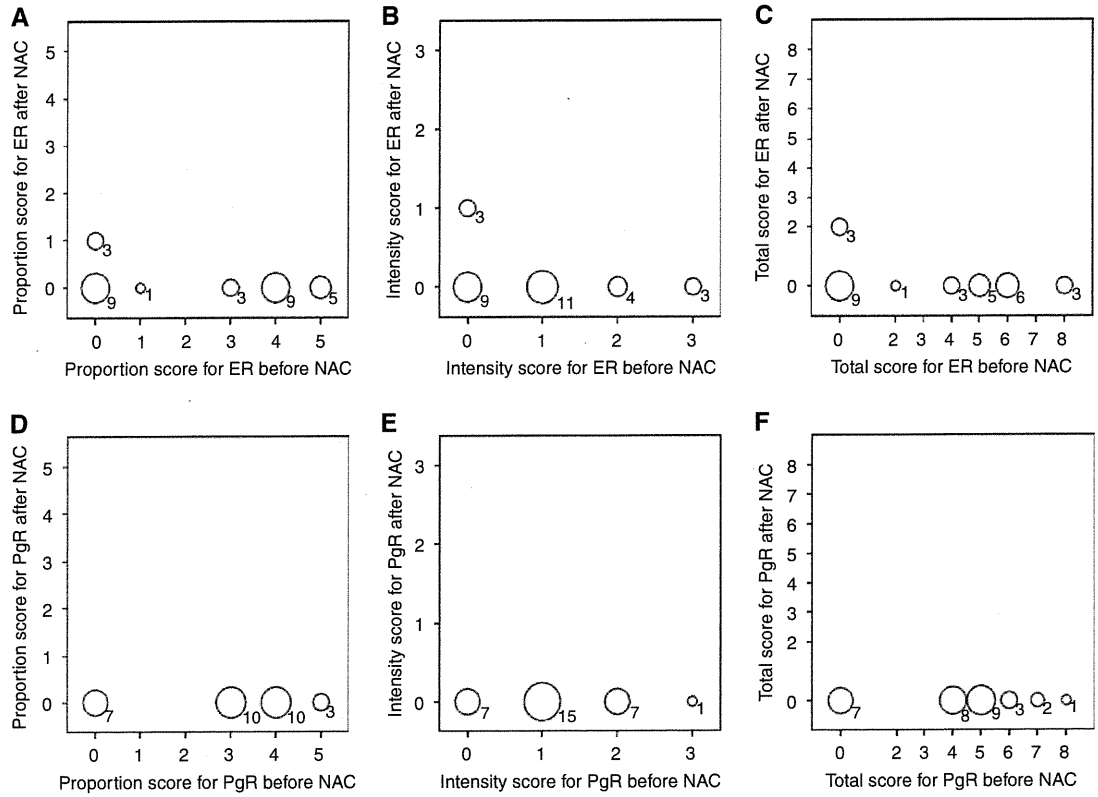

Figure 2 The distribution of scores for oestrogen receptor and progesterone receptor staining before and after neoadjuvant chemotherapy in 30 patients whose lesions changed from hormone receptor (HR)-positive status to HR-negative status. The size of the circle indicates the number of patients and the number is below the circle. (**A–C**) Proportion score, intensity score and total score of ER before and after NAC. (**D–F**) Proportion score, intensity score and total score of PgR befoe and after NAC.

as determined by the log-rank test ($P=0.008$). The 3-year DFS rates in Groups A, B, C, and D were 80.3, 78.4, 36.4, and 72.2%, respectively.

Table 4 shows the results of the multivariate Cox regression analysis of DFS with stepwise selection. The following six variables were chosen as prognostic factors for inclusion in the Cox proportional hazard model: age (<35 *vs* ⩾35 years), clinical stage at diagnosis (IIA and IIB, or IIIA *vs* IIIB or IIIC), histological grade (1 *vs* 2 and 3), HER2 status (positive *vs* negative), clinical response (CR, PR *vs* SD, PD), and the number of lymph node metastases (0 *vs* 1–3 *vs* ⩾4). Three of these variables—the HER2 status, clinical response to NAC, and the number of lymph node metastases—were identified by the stepwise selection method in the multivariate Cox regression model as the variables affecting the DFS.

The DFS of Groups B and A was similar (hazard ratio, 1.16; 95% CI, 0.61–2.19), whereas that of Group C was significantly shorter than that of Group A (hazard ratio, 6.88; 95% CI, 3.00–15.80). Table 5 summarises the results of the analysis of the efficacy of ET in the 59 patients who showed HR status conversion by using the multivariate Cox regression model. The DFS of the ET-administered patients was significantly longer than that of ET-naive patients (hazard ratio, 0.19; 95% CI, 0.06–0.60; $P<0.004$).

Figure 6 shows the Kaplan–Meier curves for OS in the four groups. The differences among the four curves were statistically significant, as determined by the log-rank test ($P=0.035$). The 5-year survival rates of Groups A, B, C, and D were 90.3, 86.3, 58.9, and 78.2%, respectively. The pattern of results of the analyses for OS in the four groups was similar to that for DFS.

DISCUSSION

This is the first report on the long-term outcomes and impact of adjuvant ET in patients with HR status conversion after NAC. In this study, the DFS and the OS of ET-administered patients with HR status-converted lesions were similar to those of ET-administered patients with lesions that were HR-positive both before and after NAC, whereas the DFS of ET-naive patients whose lesions show HR status conversion was significantly shorter than that of ET-administered patients whose lesions were HR-positive both before and after NAC. Analysis of OS yielded results similar to that pertaining to DFS. These findings indicate that the change in the status alone did not seem to influence the long-term outcome; rather, the non-administration of adjuvant ET seemed to be associated with a worse prognosis.

ER, PgR, and HER2 status changes were observed in 14.9, 29.1, and 9.5% of the patients included in our study. The overall frequency of patients with HR status conversion was 16.0%. This incidence of HR status conversion was similar to previous reports on post-NAC change in the ER, PgR, and HER2 statuses, which reported incidences of 8–28%, 6–59% (Bottini *et al*, 1996; Lee *et al*, 2003; Taucher *et al*, 2003; Colleoni *et al*, 2004; Burcombe *et al*, 2005; Shet *et al*, 2007; Kasami *et al*, 2008; Neubauer *et al*, 2008), and 0–21% (Bottini *et al*, 1996; Colleoni *et al*, 2004; Arens *et al*, 2005; Burcombe *et al*, 2005; Quddus *et al*, 2005; Adams *et al*, 2008; Kasami *et al*, 2008; Neubauer *et al*, 2008), respectively. Although the rate of cases with no change in the HR status after NAC was high, the incidence of change in the HR status is

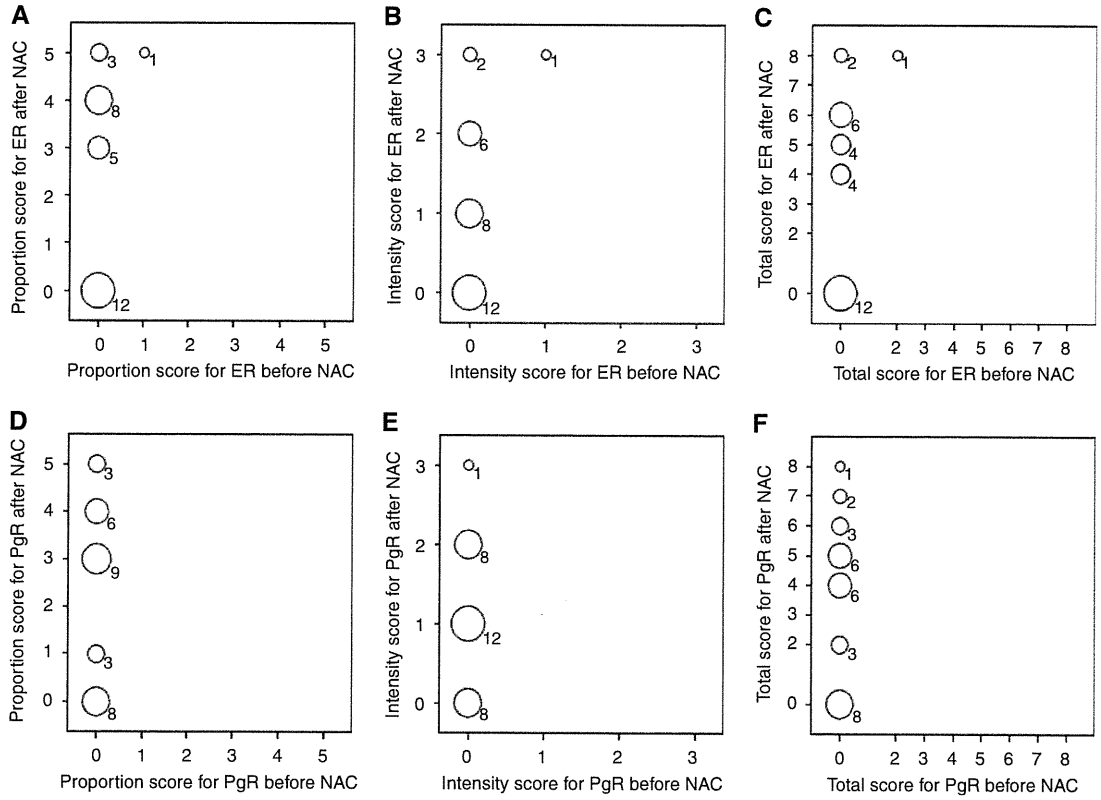

Figure 3 Scores of staining for oestrogen receptor and progesterone receptor before and after neoadjuvant chemotherapy in 29 patients whose lesions changed from being hormone receptor (HR)-negative to HR-positive. The size of the circle indicates the number of patients and the number is below the circle. (**A**–**C**) Proportion score, intensity score, total score of ER before and after NAC. (**D**–**F**) Proportion score, intensity score, total score of PgR before and after NAC.

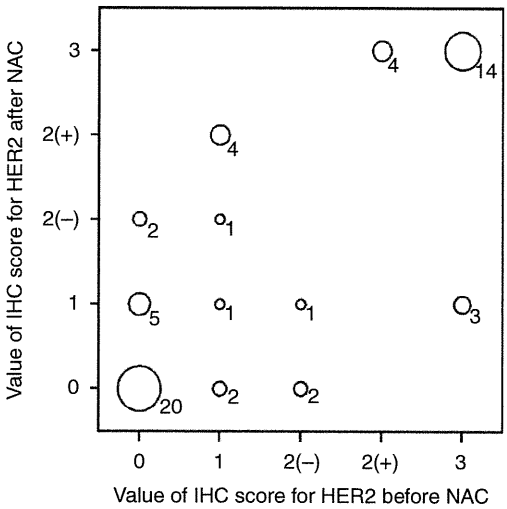

Figure 4 Bubble plot for immunohistochemistry score for HER2 before and after neoadjuvant chemotherapy in 59 patients with hormone receptor status conversion. The figures added to the bubbles are the number of patients and each bubble's size is determined by the number of patients in the category: the more the patients, the larger the bubble. The symbols (+) and (−), respectively, indicate the positive and negative status by fluorescent *in situ* hybridisation (FISH).

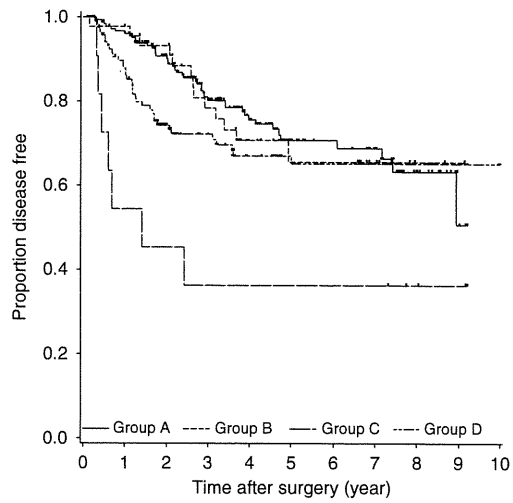

Figure 5 Kaplan–Meier curves of disease-free survival in four groups. Short vertical lines indicate censored data points. Log-rank test was significant for disease-free survival (DFS) ($P = 0.008$).

clinically not negligible. The poor prognosis of patients with HR status conversion not administered adjuvant ET indicates the necessity to determine the HR status of the lesions both before and after NAC and to administer ET to patients with HR status conversion.

Despite yielding these clinically relevant findings, our study is limited in some aspects: (1) The patient groups studied were heterogeneous in terms of sample size and characteristics. (2) This study was retrospective and the results of the statistical tests were not based on randomisation, but were exploratory, although the

Table 4 Results of multivariate Cox regression analysis of disease-free survival with stepwise selection

Variables	Hazard ratio (95% CI)	*P*-value
Group		
A	1	
B	1.16 (0.61, 2.19)	0.652
C	6.88 (3.00, 15.80)	<0.001
D	1.63 (1.01, 2.63)	0.045
Clinical stage		
IIA/IIB/IIIA	1	
IIIB/IIIC	1.56 (1.00, 2.42)	0.049
HER2		
Negative	1	
Positive	2.00 (1.30, 3.09)	0.002
Clinical response		
SD/PD	1	
PR/CR	0.56 (0.34, 0.92)	0.021
Number of lymph node metastases		
0	1	
1–3	2.09 (1.14, 3.83)	0.017
>4	6.49 (3.71, 11.37)	<0.001

Abbreviations: CI = confidence interval; CR = complete response; PR = partial response; SD = stable disease; PD = progression disease.

Table 5 Efficacy of endocrine therapy in patients with lesions showing hormone receptor status conversion after neoadjuvant chemotherapy in terms of disease-free survival

Variables	Hazard ratio (95% CI)	*P*-value
ET		
No	1	
Yes	0.19 (0.06, 0.60)	0.004
HER2		
Negative	1	
Positive	1.58 (0.46, 5.42)	0.467
Clinical response		
SD/PD	1	
PR/CR	0.75 (0.15, 3.93)	0.738
Clinical stage		
IIA/IIB/IIIA	1	
IIIB/IIIC	1.03 (0.26, 4.16)	0.968
Number of lymph node metastases		
0	1	
1–3	2.74 (0.63, 11.98)	0.181
>4	14.66 (3.24, 66.43)	0.001

Abbreviations: CI = confidence interval; CR = complete response; PR = partial response; SD = stable disease; PD = progression disease.

prognostic factors were adjusted using multivariate Cox regression analysis. Therefore, the impact of the change in the pre- and post-NAC HR statuses on the long-term outcomes and the efficacy of ET for patients with HR status conversion should be evaluated using a prospective study design. (3) The methods for measuring the ER and PgR status varied with the age of the patients, as shown in Table 1. Although the methods used for the determination of the HR statuses of the tumours of 36 patients among 368 patients were measured using different methods for the CNB and surgical specimens, only three of these tumours showed HR status conversion. A previous report showed that the HR status conversion occurred in 23% of the population in a study in which the same methods were used for the analysis of CNB and surgical specimens (Tacca *et al*, 2007), whereas HR status conversion was observed in 16.0% (59 patients) of the patients in this study. Therefore, the difference in the methods for measuring the ER and PgR statuses of the CNB and surgical specimens seems not to be the only reason for HR-status conversion.

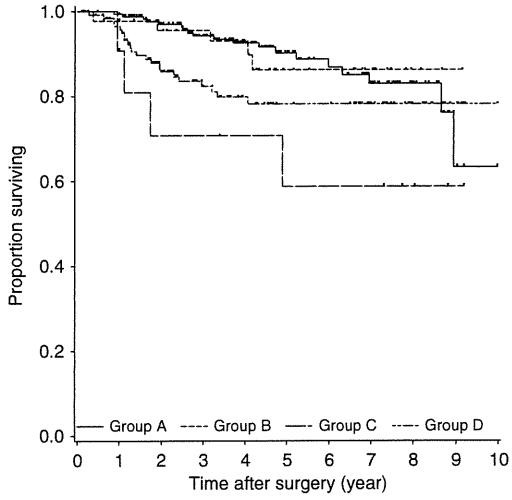

Figure 6 Kaplan–Meier curves of OS in four groups. Short vertical lines indicate censored data points. Log-rank test was significant for overall survival (OS) ($P = 0.035$).

In conclusion, our study showed that the prognosis of patients with change in HR status after NAC but who did not receive ET was worse than that of the other groups. The hormone receptor status should be evaluated not only in the biopsy specimens obtained before the initiation of NAC but also in specimens obtained during post-NAC surgery; the pre- and post-NAC HR statuses will help determine the indication for adjuvant ET in patients. ET appears to be suitable for patients with tumours positive for HR status at least once, that is, either before or after NAC.

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Conflict of interest

The authors declare that there are no competing financial interests.

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Clinicopathological Features of Tumors as Predictors of the Efficacy of Primary Neoadjuvant Chemotherapy for Operable Breast Cancer

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Abstract

Background Neoadjuvant chemotherapy (NC) is standard therapy for patients with locally advanced breast cancer and is increasingly used for early-stage operable disease. Clinical and pathological responses are important prognostic parameters for NC, which aims to achieve a pathological complete response or tumor reduction to reduce the volume of subsequent breast resection. Clinicopathological markers that predict patient response to NC are needed to individualize treatment.

Methods From 1998 to 2006, 368 patients with primary breast cancer underwent curative surgical treatment after NC (anthracycline and/or taxane without trastuzumab). We retrospectively evaluated the clinicopathological features and classification of the tumors using computed tomography (CT) before NC and analyzed the correlation with the pathological complete response (pCR) and reduction of tumor size after treatment.

Results The overall response and pCR rates in these patients were 86% and 17%, respectively. In multivariate analysis, classification as a scirrhous-type tumor was an independent predictor of reduced likelihood of pCR ($p = 0.0115$; odds ratio 0.21). For tumor reduction, histological grade 3 ($p = 0.0002$; odds ratio 3.3) and localized tumors identified by using CT imaging ($p = 0.0126$; odds ratio 2.4) were independent predictors in multivariate analysis.

Conclusions In this study, NC often did not result in pCR for breast cancers classified as scirrhous. Furthermore, tumor type classification using CT imaging and histological grading was effective to predict tumor reduction in response to NC that included an anthracycline and/or a taxane.

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Introduction

Neoadjuvant chemotherapy (NC) is used to reduce the size of locally advanced breast cancer tumors, and hence, the area to be resected, or to enable breast conservation for cases in which it was otherwise not possible. In clinical practice, because currently available anticancer drugs are extremely effective, these goals are achieved in many patients and the primary tumors completely disappear (i.e., pathological complete response (pCR)) in some patients by the end of NC. Data from large-scale studies have revealed that the patients who achieved pCR after preoperative administration of anticancer drugs have significantly better prognoses than other patients. These preoperative chemotherapy regimens primarily consist of an anthracycline. A

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.

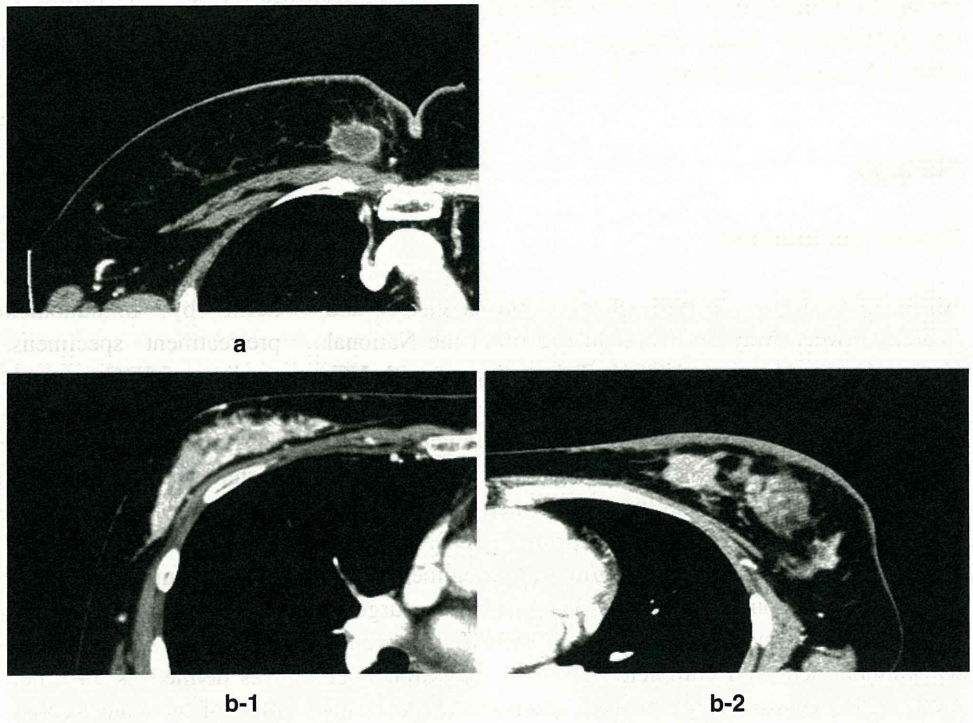

Fig. 1 Classification of tumor by CT imaging. **a** Localized type. **b-1** Nonlocalized type: glandular spreading. **b-2** Nonlocalized type: tumor with surrounding lesions

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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がん診療update

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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―

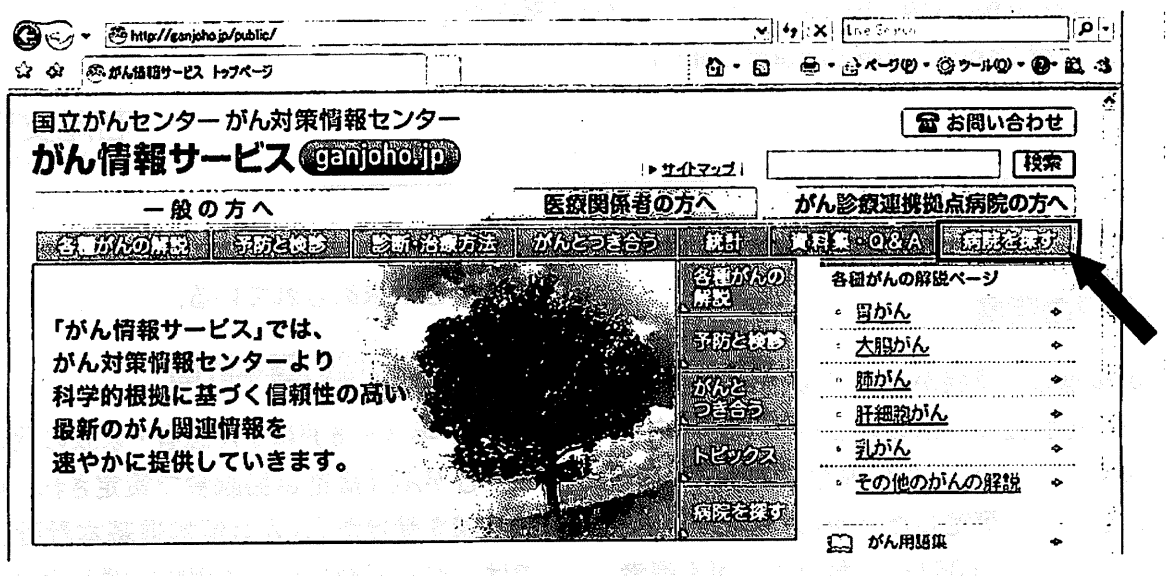

図1　がん情報サービス「一般の方へ」トップページ

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

5 がん検診・がん研究の社会的側面

1 わが国のがん対策の動向

1. がんの状況

がんは，1981(昭和56)年にわが国における死因の第1位となって以来増え続け，今や毎年およそ60万人ががんにかかり，30万人以上ががんで亡くなる状況となっている．また，男性の2人に1人，女性の3人に1人ががんにかかるといわれ，がんはわが国にとって重大な脅威となっている．

このような状況を踏まえて，2005(平成17)年5月にがん対策を総合的に推進するために，厚生労働大臣を本部長とする「がん対策推進本部」が設置され，全省的な取り組みが開始され，同年8月に「がん対策推進アクションプラン2005」が策定された．この中で，がん対策全体を国民・患者の視点から総点検し，がん対策の効果をよりいっそう高め，国民・患者のニーズに応じた対策の重点的推進を図るための「がん対策基本戦略」として再構築する（アクション1），国民・患者のがん医療に対する不安や不満の解消を推進するとともに，現場のがん医療水準の向上と均てん化を図るため，がん対策に係わる「がん情報提供ネットワーク」の構築を推進する（アクション2），国民・患者の意識やニーズ，がん医療の実態を適切に反映した情報提供ネットワークを共有するための「検討の枠組み」を創設し，国民・患者本位のがん対策を推進する（アクション3），の3つのアクションが策定された．アクション2では，様々ながん対策に関連する情報の効果的・効率的な収集・分析・発信等に不可欠な情報ネットワークの中核的組織として，国立がんセンターにがん対策情報センターを設置し，がん診療拠点病院に相談対応を担う「相談支援センター」を設置し，両者で連携して，情報提供ネットワークを構築することが謳われている．

さらに，2006(平成18)年4月には，がん対策の企画・立案・調整を行う担当部署として，厚生労働省健康局にがん対策推進室が設置された．

2. がん対策基本法

2006(平成18)年6月 がん対策基本法が議員立法によって成立した．がん対策基本法では，がん対策のいっそうの充実を図るために，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，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．基本理念は，

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，治療に係わる技術の向上その他の研究等の成果を普及し活用し発展させること

②がん患者がその居住する地域に関わらず，等しく科学的知見に基づく適切ながんに係わ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

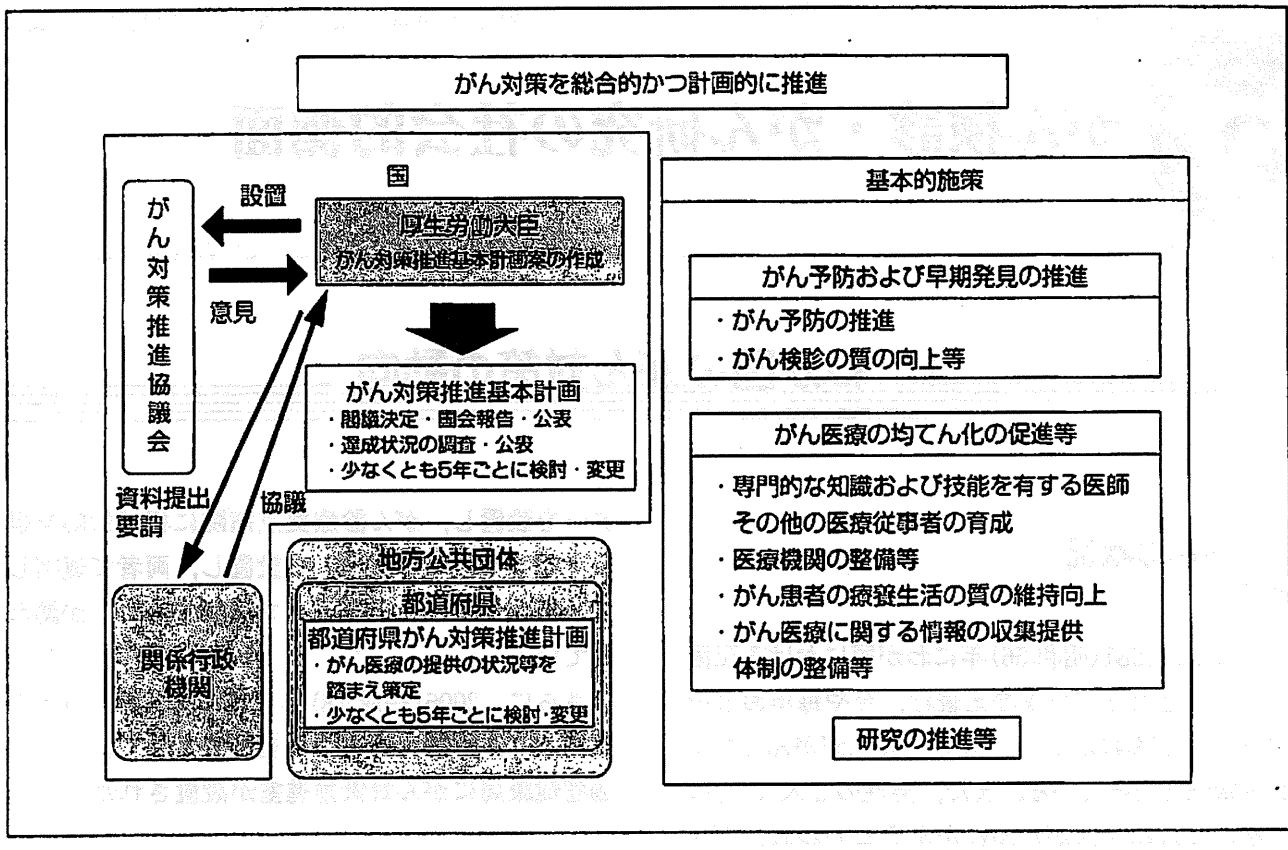

図1　がん対策基本法（平成19年4月施行）

の3点とされている．また，がん対策の総合的かつ計画的な推進を図るため，がん対策の推進に関する基本的な計画である「がん対策推進基本計画」を策定すること．そのがん対策推進基本計画を基本として，各都道府県が地域におけるがん患者に対する医療の提供の状況等を踏まえて，「都道府県がん対策推進計画」を策定することなどが謳われている．さらに，基本的施策として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，研究の推進等があげられている（図1）．

3．がん対策推進基本計画

2007（平成19）年4月1日 がん対策基本法が施行され，がん対策推進協議会が開催された．がん対策推進協議会は，がん医療に従事する者，学識経験者に加え，患者，家族の代表も含んだ委員で構成され，4～5月の短期間の集中審議によってがん対策推進基本計画を策定し，6月に閣議決定がなされた．

a）基本方針と全体目標

本計画は「がん患者を含めた国民の視点に立ったがん対策の実施」と「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」を基本方針として，重点的に取り組むべき課題として，「放射線療法及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」の3つをあげている．

本計画の全体目標は，「がんによる死亡者の減少」，「すべてのがん患者及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」の2つがあげられている．「がんによる死亡者の減少」は2005～2015年までの10年間で「がんの年齢調整死亡率（75歳未満）の20％減少」を達成することを目標としたもので，この10年間に減少が見込まれている10％に加え，喫煙率を半減することによる1.6％減少，がん検診の受診率を50％に増加させることによる4％減少，がん医療の均てん化を全がん種で達成することによる4.7％減少を合わせて，全体で20％の減少としたものである．また，

「すべてのがん患者及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」は，身体的・精神的苦痛を抱いている多くのがん患者とその家族に対して，治療の初期段階からの緩和ケアの実施，がん医療のさらなる充実，がん医療に関する相談支援や情報提供等により，実現することを目標としている．

b) 分野別施策と個別目標

分野別施策およびその成果や達成度を測るための個別目標として，分野別に現況，取り組むべき施策，個別目標があげられている．各分野の個別目標を以下に示す．

(1) がん医療

がん医療分野ではさらに細分化がなされている．

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では，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こと

②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

③在宅医療では，がん患者の意向を踏まえ，住み慣れた家庭や地域での療養を選択できる患者数の増加

④診療ガイドラインの作成では，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

がそれぞれ個別目標とされている．なお，緩和ケアの研修について，当時の安倍総理大臣の指示により，実行上5年で実施と指示されている．

(2) 医療機関の整備等

医療機関の整備等では，原則として全国すべての二次医療圏において，3年以内におおむね1ヵ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．

(3) がん医療に関する相談支援および情報提供

相談支援および情報提供では，原則として全国すべての二次医療圏において，3年以内に相談支援センターをおおむね1ヵ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．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とされている．

(4) がん登録

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は，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目標とされている．さらに，がん登録に対する国民の認知度調査を行うとともに，がん登録のあり方について更なる検討を行い，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．

(5) がんの予防

がんの予防では，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更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．

(6) がんの早期発見

早期発見では，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年以内にがん検診の受診率を50%以上とすることが目標とされている．

(7) がん研究

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

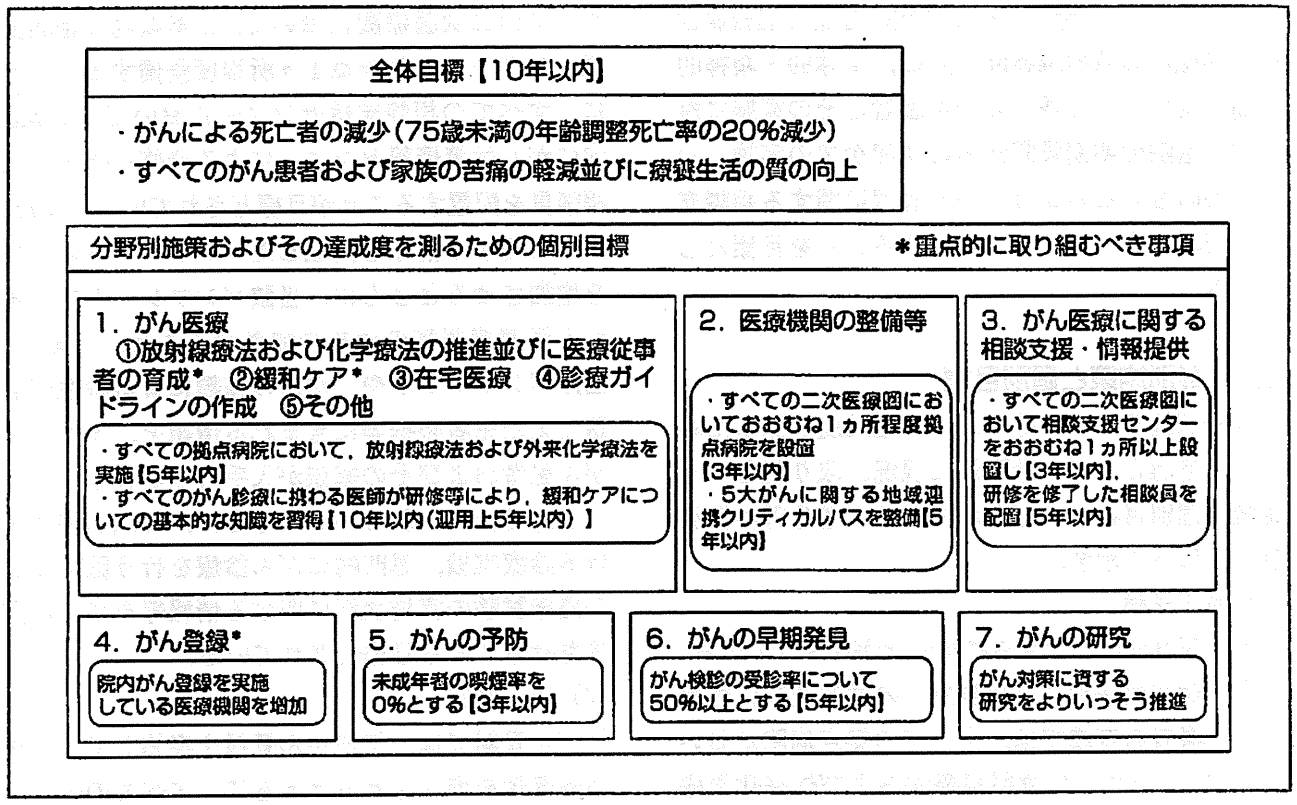

図2 がん対策推進基本計画

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いっそう推進していくことが目標とされている(図2)．

4．都道府県がん対策推進計画

国レベルのがん対策推進基本計画に基づき，各都道府県が地域の医療資源を踏まえて策定する計画である．2008(平成20)年3月末までに策定することが求められており，2009(平成21)年3月20日の時点で奈良県を除く46都道府県で策定されている．「都道府県がん対策推進計画」は，医療法に規定する医療計画，健康増進法に規定する都道府県健康増進計画，介護保険法に規定する都道府県介護保険事業支援計画，その他の法令の規定による保健，医療または福祉に関する事項を定める計画と調和が保たれたものであることが求められている．

5．がん診療連携拠点病院

がん診療連携拠点病院は，2001(平成13)年8月の健康局長通知「地域がん診療拠点病院の整備について」に基づき整備が開始された．その後，2006(平成18)年2月1日にアクションプラン2005を踏まえた健康局長通知により，指定要件が変更されるとともに名称が「がん診療拠点病院」から「がん診療連携拠点病院」に変更され，都道府県がん診療連携拠点病院が追加されるとともに，相談支援センターの設置が定められた．さらに，2008(平成20)年3月1日にがん対策推進基本計画を踏まえた健康局長通知により，指定要件の一部が変更された．2009(平成21)年4月1日の時点で，都道府県がん診療連携拠点病院は51病院，地域がん診療連携拠点病院は324病院，合わせて375病院が指定を受けている．

a) 地域がん診療連携拠点病院の指定要件

拠点病院は，診療機能として集学的治療の提供体制および標準的治療等の提供，化学療法の提供

体制，緩和ケアの提供体制，セカンドオピニオンの提示体制等を有することが求められている．また，医療従事者として専門的な知識および技能を有する医師，専門的な知識および技能を有するコメディカルスタッフ等を配置することが求められている．さらに，設備として放射線治療に関する機器，外来化学療法室の設置等が求められている．

また，地域医療機関等に対する研修として，がん医療に携わる医師を対象とした緩和ケアに関する研修，早期診断および緩和ケア等に関する研修の実施，および診療連携を行っている地域の医療機関等の医療従事者も参加する合同のカンファレンスの開催が求められている．

情報の収集提供体制として，相談支援センターを設置して，がん対策情報センターが実施する研修を修了した相談員を配置し，院内および地域の医療従事者の協力を得て，院内外のがん患者およびその家族並びに地域の住民および医療機関などからの相談に対応する体制を整備することなどが求められている．また院内がん登録として，「標準登録様式」に基づく院内がん登録の実施，がん対策情報センターにおける研修を受講したがん登録実務者の配置，院内がん登録の集計結果などのがん対策情報センターへの提供等が求められている．

b）特定機能病院を地域がん診療連携拠点病院として指定する場合の指定要件

特定機能病院を指定する場合は，組織上明確に位置付けられた複数種類のがんに対し放射線療法を行う機能を有する部門，および組織上明確に位置付けられた複数種類のがんに対し化学療法を行う機能を有する部門をそれぞれ設置し，当該部門の長として専任の放射線療法または化学療法に携わる専門的な知識および技能を有する常勤の医師をそれぞれ配置することが求められている．

c）都道府県がん診療連携拠点病院の指定要件について

都道府県がん診療連携拠点病院の場合は，放射線療法部門および化学療法部門をそれぞれ設置し，当該部門の長として専任の放射線療法または化学療法に携わる専門的な知識および技能を有する常勤の医師をそれぞれ配置すること，当該都道府県において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・薬剤師・看護師等を対象とした研修を実施すること，地域がん診療連携拠点病院等に対し，情報提供，症例相談および診療支援を行うことなどが求められている．さらに，都道府県がん診療連携拠点病院は，都道府県がん診療連携協議会を設置し，

①当該都道府県におけるがん診療の連携協力体制および相談支援の提供体制その他のがん医療に関する情報交換
②当該都道府県内の院内がん登録のデータの分析，評価
③がんの種類ごとに，当該都道府県においてセカンドオピニオンを提示する体制を有するがん診療連携拠点病院を含む医療機関の一覧の作成・広報
④当該都道府県におけるがん診療連携拠点病院への診療支援を行う医師の派遣に係る調整
⑤当該都道府県におけるがん診療連携拠点病院が作成している地域連携クリティカルパスの一覧を作成・共有
⑥当該都道府県におけるがん診療連携拠点病院が実施するがん医療に携わる医師を対象とした緩和ケアに関する研修，その他各種研修に関する計画を作成

などを実施することが求められている．

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1) がん対策推進アクションプラン 2005 (http://www.mhlw.go.jp/bunya/kenkou/gan01/index.html)
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