[12] treatment settings. Therefore, AIs in combination with ovarian suppression have been evaluated for the treatment of premenopausal women with ER-positive breast cancer.[13,14]

Neoadjuvant treatment for breast cancer provides an opportunity for downstaging of large tumors to allow patients to undergo breast-conserving surgery rather than mastectomy. Chemotherapy can offer an effective neoadjuvant treatment; however, increasing evidence suggests that ER-positive tumors are less sensitive to chemotherapy.[15] It has been demonstrated that neoadjuvant endocrine therapy has efficacy in the treatment of ER-positive disease among postmenopausal women, resulting in similar objective response rates and rates of breast-conserving surgery for AIs compared with more cytotoxic chemotherapy.[16] Therefore, the role of neoadjuvant endocrine therapy in premenopausal women is also of interest.

With the increasing costs associated with large-scale adjuvant trials, both the prognostic value of biologic markers and the long-term predictive value of short-term trials are increasingly important. The expression of nuclear antigen Ki-67, a marker of cell proliferation, reportedly has been correlated with treatment efficacy and is being investigated for its value as a predictive marker of therapeutic response.[17] In a cross-trial comparison, an increased reduction in Ki-67 expression after neoadjuvant treatment with anastrozole compared with tamoxifen was observed consistently; and increased progression-free survival has been reported for anastrozole versus tamoxifen in the adjuvant Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial.[8,18,19]

The STAGE study (Study of Tamoxifen or Arimidex Combined With Goserelin Acetate to Compare Efficacy and Safety) was the first randomized trial to compare anastrozole plus goserelin versus tamoxifen plus goserelin in the neoadjuvant setting (24 weeks of therapy) in premenopausal women with ER-positive and human epidermal growth factor receptor 2 (HER2)-negative, operable breast cancer. The patients who received anastrozole plus goserelin in that trial had a superior best overall tumor response compared with the patients who received tamoxifen plus goserelin, as measured on magnetic resonance imaging (MRI) or computed tomography (CT) studies (anastrozole plus goserelin, 64.3%; tamoxifen plus goserelin, 37.4%; estimated difference, 26.9%; 95% confidence interval [CI], 13.5-40.4; $P < .001$). The treatment effect was consistently in favor of anastrozole, regardless of the measurement methods (caliper and ultrasound). The histopathologic response rate also was better in the anastrozole group (anastrozole plus goserelin, 41.8%; tamoxifen plus goserelin, 27.3%; estimated difference, 14.6%; 95% CI, 1.4-27.7; $P = .032$). Both treatment regimens were well tolerated, consistent with the known safety profiles of anastrozole, tamoxifen, and goserelin.[20] The geometric mean Ki-67 index at baseline was 21.9% in the anastrozole group and 21.6% in the tamoxifen group. At week 24, the Ki-67 index was reduced in both treatment groups (to 2.9% in the anastrozole group and to 8% in the tamoxifen group). The reduction from baseline to week 24 was significantly greater with anastrozole than with tamoxifen. The estimated ratio of reduction between groups was 0.35 (95% CI, 0.24-0.51; $P < .001$).[20] Here, we report an exploratory analysis of the STAGE study that investigated potential correlations between the Ki-67 index and the best overall tumor response, ER status, PgR status, or histopathologic response.

MATERIALS AND METHODS

Study Design and Patients

In this phase 3, double-blind, randomized, parallel-group, multicenter trial, the participating patients were premenopausal women ≥20 years with ER-positive and HER2-negative breast cancer who had operable and measurable lesions (tumors measuring 2-5 cm, negative lymph node status [N0], and no metastases [M0]). Inclusion and exclusion criteria have been described previously.[20]

Patients were randomized 1:1 to receive either oral anastrozole 1 mg daily with a tamoxifen placebo or oral tamoxifen 20 mg daily with an anastrozole placebo. Both treatment groups received goserelin 3.6 mg as a subcutaneous injection every 28 days. Treatment continued for 24 weeks before surgery or until patients met any criterion for discontinuation.

The primary study endpoint was the best overall tumor response during the 24-week neoadjuvant treatment period. Secondary endpoints included histopathologic response, changes in estrone (E_1) and estradiol (E_2) serum and breast tumor tissue concentrations, changes in Ki-67 expression, and tolerability. For this exploratory analysis, we assessed correlations between Ki-67 expression and tumor response, ER status, PgR status, or histopathologic response.

The protocol was approved by an institutional review board at all study sites, and all enrolled patients provided written informed consent. The study (National Clinical Trials identifier NCT00605267) was conducted in accordance with the Declaration of Helsinki and good clinical practice, the applicable local regulatory requirements, and the AstraZeneca policy on Bioethics.

Assessments

Tumor measurements were performed using caliper measurements, ultrasound, or MRI or CT studies. The

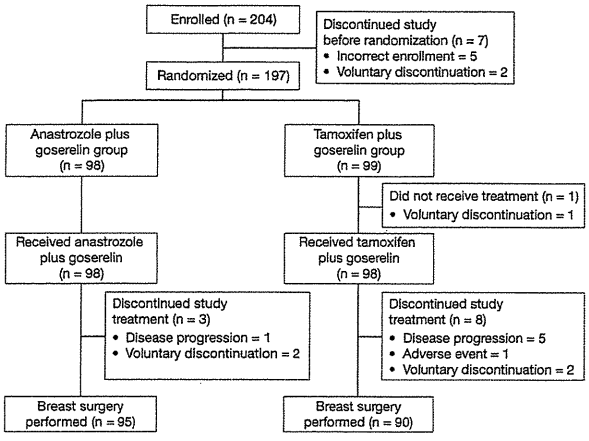

Figure 1. This is a CONSORT (Consolidated Standards of Reporting Trials) diagram of the current study.

primary analysis indicated that the best overall tumor response for anastrozole versus tamoxifen was consistent, regardless of the measurement method used.[20] We present tumor response data from the MRI or CT measurements at day 0 and at 24 weeks. The objective tumor response was assessed according to modified Response Evaluation Criteria in Solid Tumors (RECIST).[21]

The status of Ki-67, ER, and PgR was determined using histopathologic core-needle biopsy specimens that were collected at baseline and at surgery. Tissue sections were fixed in formalin and stored at room temperature before immunohistochemical staining. Ki-67 expression was determined by staining sections with an anti-MIB-1 antibody at a central laboratory (SRL Inc., Tokyo, Japan) for assessment by a central review board. For all slides, photomicrographs were taken from 3 to 5 hotspots at ×20 magnification using light microscopy. Two pathologists independently assessed the photomicrographs, and the Ki-67 index was calculated as the ratio of Ki-67-positive cancer cells from a total of 1000 cancer cells. ER-positive status and PgR-positive status at baseline were defined as ≥10% staining of cancer cell nuclei determined by a pathologist at each individual study site (nuclei were assessed using mouse monoclonal antibody clones 6F11 and 16, respectively). Staining for ER and PgR also was assessed in parallel using Allred scores by the Central Pathologist Review Committee.[22] An Allred score (the proportion score plus the intensity score) of ≥3 defined ER or PgR positivity, a score from ≥3 to <7 indicated medium expression, and a score of ≥7 indicated rich expression.

Histopathologic effects were assessed by comparing histopathologic samples that were obtained at baseline and at surgery. For the assessment of histopathologic response, the following categories were used: grade 0 indicated no response; grade 1a, marked change in <1 of 3 cancer cells; grade 1b, marked changes in ≥1 of 3 but <2 of 3 cancer cells; grade 2, marked changes in ≥2 of 3 cancer cells; and grade 3, necrosis or disappearance of all cancer cells and replacement of all cancer cells by granuloma-like and/or fibrous tissue. The histopathologic response was defined as the proportion of patients whose tumors were classified as grade 1b, 2, or 3.[23,24]

Post hoc subset analyses were used to determine correlations between the baseline Ki-67 index (≥20% vs <20%) and the best overall tumor response. The percentage change in the Ki-67 index for responders (patients whose best overall tumor response was a complete or partial response) versus nonresponders (patients whose best overall tumor response was stable or progressive disease) also was compared. Correlations between the baseline Ki-67 index and the histopathologic response at week 24 also were evaluated, and we used post hoc analyses to investigate correlations between changes in the Ki-67 index from baseline to week 24 and ER or PgR status at baseline. Positive ER and PgR status (Allred score ≥3) also was assessed at baseline and at week 24. Preoperative Endocrine Prognostic Index (PEPI) scores, which were calculated post hoc as the sum of risk points weighted by the size of the hazard ratio for tumor size, pathologic lymph node status, ER status, and Ki-67 expression for both recurrence-free and breast cancer-specific survival, were determined for each patient at surgery according to the methods described by Ellis and colleagues.[25]

Statistical Analysis

The sample size calculation and the main statistical analyses have been described previously.[20] All randomized patients were included in the intent-to-treat analysis set.

In a post hoc exploratory analysis, chi-square tests were performed to compare the best overall tumor response at week 24 between baseline Ki-67 index categories (≥20% vs <20%) within each treatment group and between treatment groups within each baseline Ki-67 index category. A chi-square test also was used to compare the histopathologic response at 24 weeks between the baseline Ki-67 index categories within each treatment group. All tests were made at the nominal 2-sided significance level of .05.

RESULTS

Patients

In total, 197 patients were randomized to receive either anastrozole plus goserelin (n = 98) or tamoxifen plus goserelin (n = 99) (Fig. 1). Patient demographics and

TABLE 1. Patient Demographics and Baseline Tumor Characteristics

Characteristic	No. of Patients (%)	
	Anastrozole Plus Goserelin	Tamoxifen Plus Goserelin
No. of patients	98	99
Age: Median [range]	44 [28-54]	44 [30-53]
Body mass index: Mean±SD, kg/m^2	22.2±3.5	22.1±3.3
Histology type		
Infiltrating ductal carcinoma	87 (88.8)	91 (91.9)
Infiltrating lobular carcinoma	3 (3.1)	3 (3)
Other[a]	8 (8.2)	5 (5.1)
Tumor grade		
1	42 (42.9)	48 (48.5)
2	36 (36.7)	26 (26.3)
3	4 (4.1)	14 (14.1)
Not assessable	1 (1)	0 (0)
Not done	15 (15.3)	11 (11.1)
Hormone receptor status		
ER positive	98 (100)	99 (100)
PgR positive	93 (94.9)	87 (87.9)
HER2 negative	98 (100)	99 (100)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; SD, standard deviation.
[a] Other included adenocarcinoma (n = 3).

baseline characteristics generally were well balanced between the treatment groups (Table 1). Paired samples for calculating changes in the Ki-67 index from baseline to week 24 were available for 89 patients in the anastrozole plus goserelin group and for 86 patients in the tamoxifen plus goserelin group.

Correlation of the Baseline Ki-67 Index and Best Overall Tumor Response

With a mean baseline Ki-67 index of 21.9% and 21.6% in the anastrozole and tamoxifen treatment groups, respectively, we used post hoc subset analyses to compare patients according to their baseline Ki-67 index (≥20 vs <20%). For anastrozole versus tamoxifen, best overall tumor response from baseline to week 24 was better with anastrozole plus goserelin versus tamoxifen plus goserelin both in patients who had a baseline Ki-67 index ≥20% (73.2% vs 44.8%; $P = .002$) and in patients who had a baseline Ki-67 index <20% (52.5% vs 29%; $P = .035$) (Fig. 2A).

Within the treatment groups, the best overall tumor response from baseline to 24 weeks, as measured by MRI or CT, was significantly better with anastrozole plus goserelin for patients who had a baseline Ki-67 index ≥20% than for those who had a baseline Ki-67 index <20% (73.2% vs 52.5%; $P = .036$). Among patients in the tamoxifen plus goserelin group, the best overall tumor response was 44.8% for patients who had a baseline Ki-67 index ≥20% and 29% for those who had a baseline Ki-67 index <20% ($P = .118$) (Fig. 2A).

Correlation of the Baseline Ki-67 Index and Histopathologic Response

There was no significant difference in the histopathologic response between patients who had a baseline Ki-67 index ≥20% versus patients who had a baseline Ki-67 index <20% in either treatment group (Fig. 2B).

Correlation of Change in the Ki-67 Index and Responders/Nonresponders

A waterfall plot of changes in the Ki-67 index for individual patients, illustrated according to responders or nonresponders, is provided in Figure 3. There was no apparent relation between a change in Ki-67 expression from baseline to week 24 for responders and nonresponders in either treatment group.

Correlation of the Baseline Ki-67 Index and Estrogen Receptor or Progesterone Receptor Status

In both treatment groups, positive ER status, as determined by the Allred score, was observed in 100% of patients at baseline and at week 24, and >90% of patients in both treatment groups were ER rich (baseline Allred score, ≥7). Therefore, it was not possible to determine any potential relation between the baseline ER Allred score and the percentage change in Ki-67 expression from baseline to week 24 in either treatment group.

In the anastrozole plus goserelin group, 98.9% of patients were positive for PgR expression at baseline, and 34.4% were positive for PgR expression at week 24. The percentage of patients with positive PgR status was not altered from baseline (91.9%) to week 24 (89.5%) in the tamoxifen plus goserelin group (Fig. 4A). In both treatment groups, the mean decrease in the Ki-67 index was greater in patients who had a baseline PgR Allred score ≥7 (anastrozole group, −88.8%; tamoxifen group, −67.6%), compared with patients who had a baseline PgR Allred score <7 (anastrozole group, −74.1%; tamoxifen group, −32.8%) (Fig. 4B).

Preoperative Endocrine Prognostic Index Score

In the anastrozole treatment group, 33.3% of patients had a PEPI score of 0 compared with 11.4% in the tamoxifen group. Fewer patients (21.4%) had a PEPI score ≥4 in the anastrozole group compared with patients in the tamoxifen group (36.7%; $P = .002$) (Table 2).

DISCUSSION

In this exploratory analysis, we investigated changes in Ki-67 expression among patients from the STAGE study, a

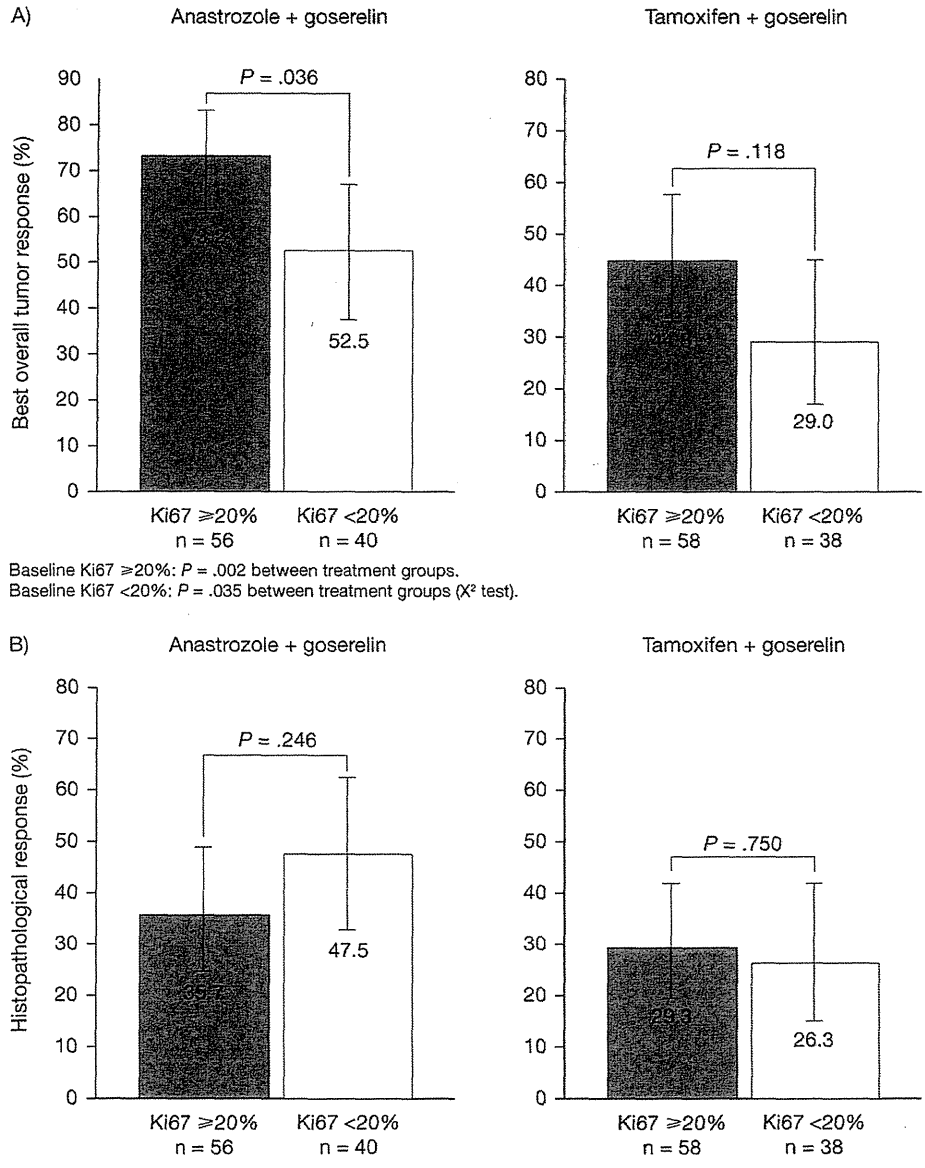

Figure 2. These charts illustrate the baseline Ki-67 index (≥20% vs <20%) according to (A) the best overall tumor response and (B) the histopathologic response at 24 weeks. Magnetic resonance imaging or computed tomography was used to measure responses. The best tumor response was defined a complete or partial response during the 24-week treatment period.

phase 3 randomized trial that compared tumor response for anastrozole plus goserelin versus response tamoxifen plus goserelin during 24 weeks of neoadjuvant treatment in premenopausal women with ER-positive breast cancer. The primary analysis indicated that the reduction in the Ki-67 index for patients who received goserelin was greater with anastrozole coadministration compared with tamoxifen, suggesting a greater inhibitory effect on tumor cell proliferation with this treatment combination.[20] Given the reported clinical prognostic value of Ki-67 expression after short-term neoadjuvant endocrine therapy for breast cancer,[19] this is in concordance with our finding that anastrozole combined with goserelin demonstrates a superior best overall tumor response compared with tamoxifen plus goserelin. Although Ki-67 is perceived as a reliable predictive endpoint, the outcomes of

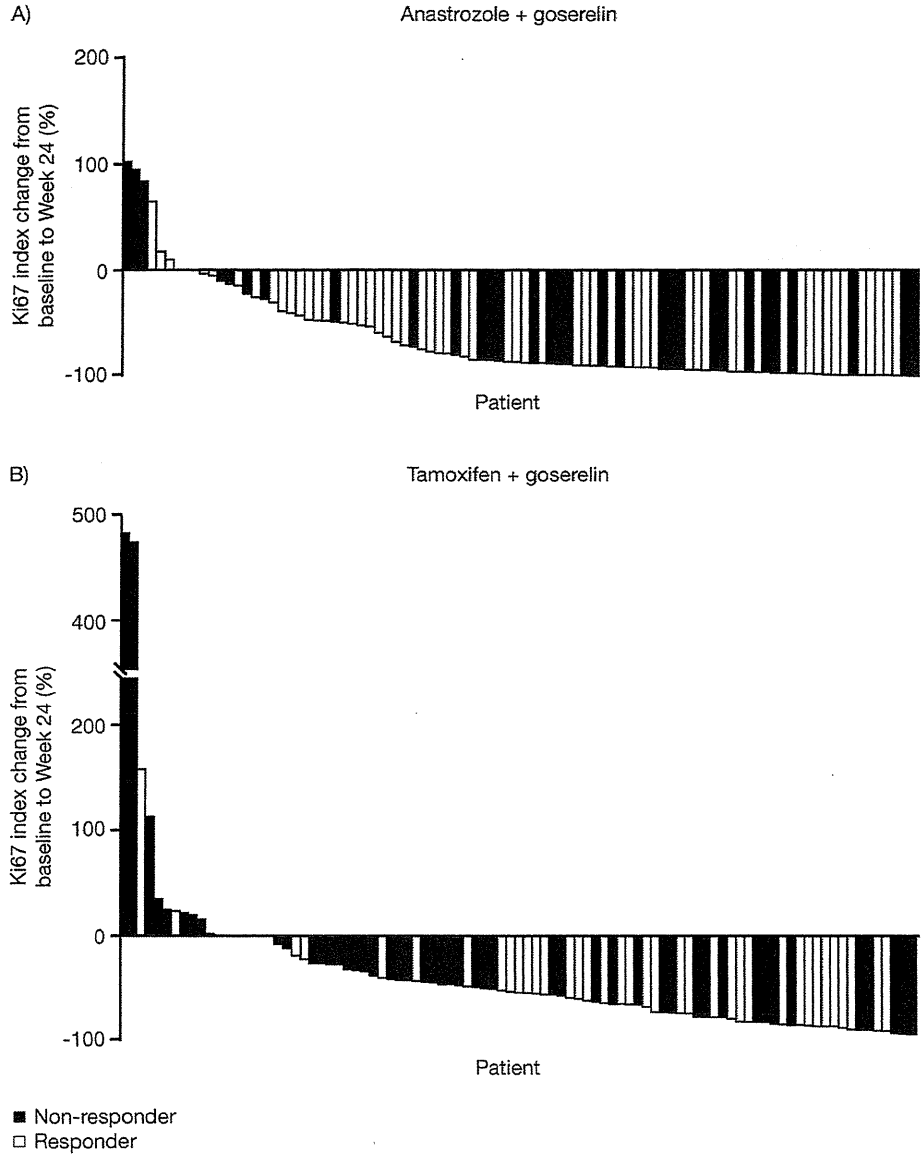

Figure 3. This is a waterfall plot of reductions in nuclear antigen Ki-67 levels in (A) the anastrozole plus goserelin treatment group and (B) the tamoxifen plus goserelin treatment group. Magnetic resonance imaging or computed tomography was used to measure responses. Responders were defined as those patients who had a complete or partial response during the 24-week treatment period.

the parallel adjuvant trial by the Austrian Breast and Colorectal Cancer Study Group (ABCSG) did not reflect outcomes related to the Ki-67 changes we observed: Results from the ABCSG-12 study indicated that there was no difference in disease-free survival between patients who received anastrozole versus tamoxifen (hazard ratio, 1.08; 95% CI, 0.81-1.44; $P = .591$).[26] The reason for this difference is not clear, although there were differences in the baseline characteristics of patients in each study: the STAGE study assessed a more hormone-dependent phenotype of tumor (ER-positive/HER2-negative in the STAGE study vs ER-positive/HER2-negative and ER-positive/HER2-positive in the ABCSG-12 trial), and the proportion of women with a body mass index >25 kg/m^2 was lower in the STAGE study (17% vs 33%). The ABCSG-12 group did not assess Ki-67 levels. It is also interesting to note that, as recently pointed out by Goncalves et al,[27] in our study, serum estradiol suppression

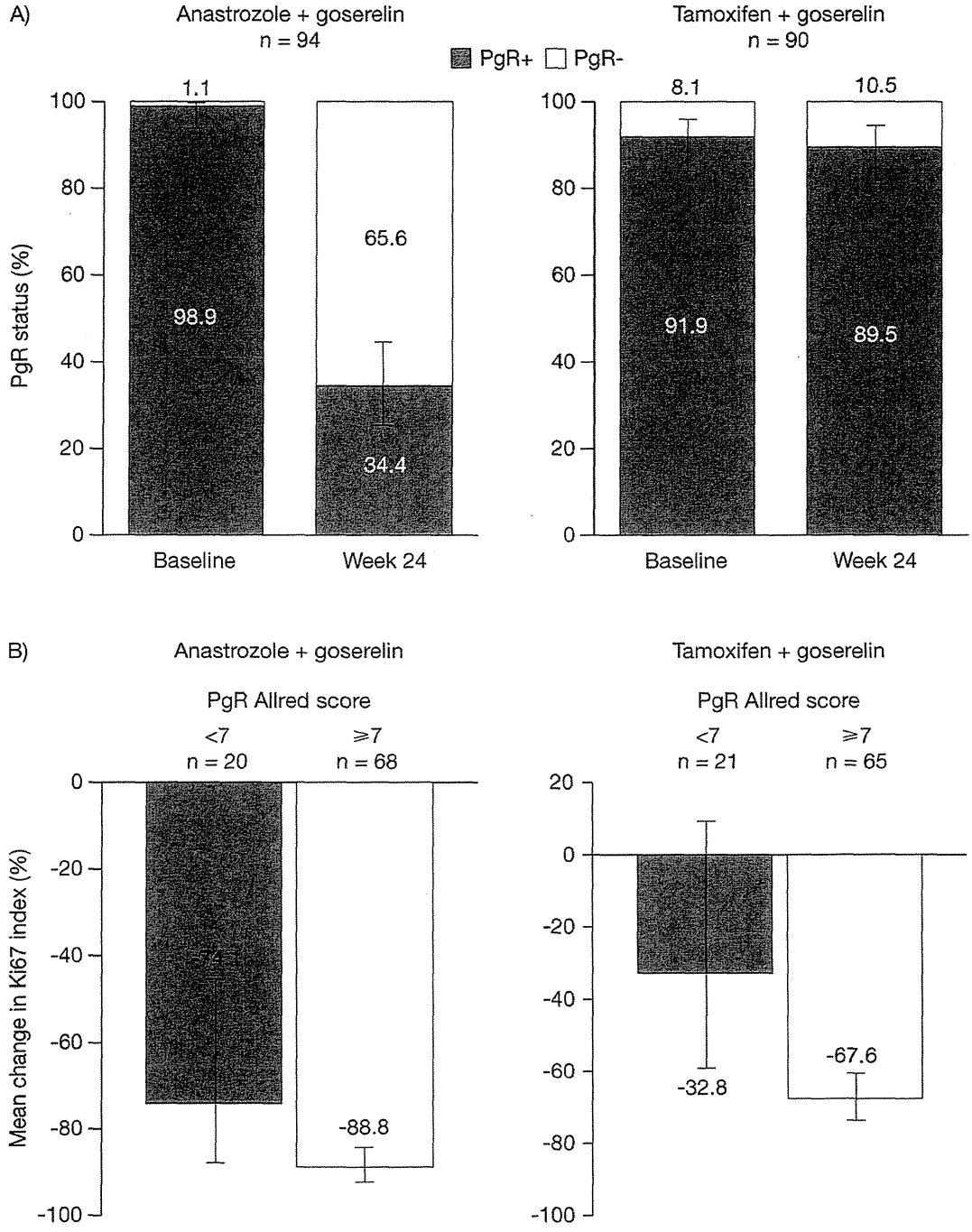

Figure 4. (A) Progesterone receptor status is illustrated at baseline and at 24 weeks. (B) Changes in the Ki-67 index and the baseline PgR Allred score are illustrated. PgR-positive (PgR+) indicates an Allred score >3; PgR-negative (PgR−), an Allred score <2.

appeared to decrease at week 24 compared with week 4, although the suppression was not statistically significant. This suggests the possibility of a gradual tachyphylaxis of the estrogen-suppressing effects of combined goserelin and anastrozole treatment, which potentially may explain the difference in outcomes between the ABCSG-12 and STAGE studies. However, further investigations would be required to confirm this.

TABLE 2. Preoperative Endocrine Prognostic Index Score

Treatment Group	No. of Patients	PEPI Score: No. of Patients (%)		
		0	1-3	≥4
Anastrozole plus goserelin	84	28 (33.3)	38 (45.2)	18 (21.4)
Tamoxifen plus goserelin	79	9 (11.4)	41 (51.9)	29 (36.7)
P for anastrozole vs tamoxifen		—	—	.002

Abbreviation: PEPI, Preoperative Endocrine Prognostic Index.
[a]*P* values were determined using the chi-square test.

In the current study, the best overall tumor response was superior with anastrozole compared with tamoxifen, irrespective of the baseline Ki-67 index. Within the anastrozole treatment group, we observed that the best overall tumor response was significantly better in patients who had a baseline Ki-67 index ≥20% versus patients who had a baseline Ki-67 index <20%. However, in the anastrozole group, we observed a numerically lower histopathologic response in patients who had a baseline Ki-67 index ≥20% compared with those who had a baseline Ki-67 index <20%. It was reported previously that baseline Ki-67 expression was not associated with outcome after neoadjuvant endocrine treatment (including anastrozole, letrozole, and tamoxifen) in ER-positive, postmenopausal women who had breast cancer.[19,25]

There was no apparent relation between a reduction in the Ki-67 index for responders and nonresponders in either treatment group. Although there tended to be more nonresponders among patients in the tamoxifen group who had less of a reduction in the Ki-67 index, the Spearman rank-correlation between the percentage change in the Ki-67 index and the best percentage change in greatest tumor dimension for the tamoxifen group was a modest 0.314. This observation is essentially consistent with what was reported previously by Dowsett et al, who conducted a similar analysis of postmenopausal patients who received neoadjuvant tamoxifen, anastrozole, and the tamoxifen/anastrozole combination.[28] This variation in the Ki-67 index change between responders and nonresponders indicates that the mechanism of estrogen-dependent growth is heterogeneous among breast tumors. Tumor growth is determined by a balance between cell proliferation and apoptosis. Stimulation of cell proliferation by estrogen may be dominantly implicated in tumor growth in some tumors, whereas inhibition of apoptosis by estrogen may be dominantly implicated in other tumors. Thus, a responder does not necessarily have a greater reduction in the Ki-67 index compared with a nonresponder if apoptosis is induced more strongly in the former than the latter after treatment.

In the neoadjuvant setting, endocrine therapy has demonstrated greater (or equivalent) efficacy in postmenopausal women with a lower Ki-67 index.[29,30] In contrast, in our study, both anastrozole and tamoxifen produced greater response rates in premenopausal women with a higher Ki-67 index. It is therefore possible that the main pathways of proliferative stimulation (and the effectiveness of endocrine treatments) may differ between premenopausal and postmenopausal women with ER-positive breast cancer, according to their level of Ki-67 expression. In general, high Ki-67 expression is traditionally is believed to offer a poor prognosis and is predictive of response to chemotherapy regimens.[31] However, our results suggest that endocrine therapy has at least comparable effectiveness for premenopausal patients with ER-positive breast cancer who have a high Ki-67 index.

No correlation could be determined between a change in the Ki-67 index and baseline ER status in either treatment group. However, the number of patients who were identified as PgR-positive decreased at week 24 in the anastrozole treatment group, an effect that was not observed in the patients who received tamoxifen plus goserelin. PgR expression also was reduced under neoadjuvant AI treatment for breast cancer in the ABCSG 17 study, although it remains to be determined whether the down-regulation of PgR may be used as a marker of clinical efficacy.[32] In our study, the reason why the positive rate of PgR was reduced in the anastrozole plus goserelin arm compared with the tamoxifen plus goserelin arm is most likely because of the estrogenic action of tamoxifen, which would induce PgR expression.

Although there may be a potential correlation between a reduction in Ki-67 and the baseline PgR Allred score in patients who receive anastrozole plus goserelin versus tamoxifen plus goserelin, further analyses will be required to determine whether a Ki-67 reduction in patients with high baseline PgR expression translates into a clinical benefit.

After treatment with anastrozole, a lower proportion of patients had a PEPI score ≥4 (indicating a high risk of

recurrence) compared with the tamoxifen treatment group. The PEPI model has been validated previously and has indicated significant differences in recurrence-free survival in the adjuvant setting between 3 PEPI risk groups (PEPI risk scores of 0, 1-3, and $\geq$4), with a PEPI score of 0 indicating a very low risk of relapse.[25] Data from the adjuvant treatment setting will provide added knowledge for the individualization of future adjuvant treatments after neoadjuvant therapy for breast cancer.

Currently, very little is known about the prognostic effect of Ki-67 in premenopausal women. However, in 1 recent study, the prognostic significance of Ki-67 was investigated in women with ER-positive breast cancer who had received short-term presurgical tamoxifen, and Decensi and colleagues reported that the Ki-67 response was a good predictor of recurrence-free survival and overall survival.[33]

To our knowledge, this is the first randomized study to investigate the potential of Ki-67 as a clinical biomarker for AI efficacy in premenopausal women with ER-positive breast cancer. It has been demonstrated that a reduction in Ki-67 expression as a result of neoadjuvant AI treatment can be a potentially useful marker of improved surgical outcomes in postmenopausal women with ER-positive breast cancer, and such a reduction has been identified as predictive of favorable outcomes in the adjuvant treatment period.[34] A reduction in Ki-67 expression during neoadjuvant treatment reportedly was greater with anastrozole versus tamoxifen in postmenopausal women who had ER-positive breast cancer,[18] and a parallel result also was observed in the corresponding adjuvant trial, in which recurrence-free survival also was greater for those who received anastrozole.[8] Yet another similar result was observed for letrozole, in which a greater Ki-67 reduction was observed compared with tamoxifen in the neoadjuvant setting.[35] Greater clinical effectiveness also was observed for letrozole in the neoadjuvant setting, both in terms of the objective response rate and the rate of breast-conserving surgery.[36]

In conclusion, tumor response was greater with anastrozole compared with tamoxifen, regardless of the baseline Ki-67 index, in premenopausal women who received goserelin as neoadjuvant therapy for ER-positive, early stage breast cancer. The current results indicate that endocrine therapy may offer a more tolerable treatment option than cytotoxic chemotherapy as neoadjuvant treatment for these patients, and further studies of the anastrozole plus goserelin treatment combination in this setting are warranted.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Iwase has received honoraria from AstraZeneca and research funding from AstraZeneca; Chugai Pharmaceutical Company, Ltd.; Novartis; and Takeda. Mr. Hayashi is an employee and holds stock ownership with AstraZeneca. Dr. Noguchi has received honoraria and research funding from and has acted in a consultant or in an advisory role for AstraZeneca.

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Diffusion pattern of low dose rate brachytherapy for prostate cancer in Japan

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Permanent implant brachytherapy for prostate cancer using iodine-125 seeds was adopted in Japan in 2003. Here, we report on the diffusion pattern of this treatment in Japan since 2003. We examined the annual numbers of prostate cancer patients per hospital in Japan, who were treated with iodine-125 seed implant brachytherapy with or without external beam radiation therapy between 2003 and 2011. The hospitals were excluded from the count if brachytherapy was begun in a hospital within the given year, and thus was only available for part of the year. In 2004, 269 patients were treated by brachytherapy at only two hospitals. However, the numbers increased rapidly. A total of 1412 patients were treated at 23 hospitals in 2005, 2783 patients were treated at 83 hospitals in 2008, and 3793 patients were treated at 109 hospitals in 2011. The mean/median numbers of patients treated per hospital were 61.4/42 in 2005, 33.5/25 in 2008, and 35.0/24 in 2011. The number of hospitals where 24 or fewer patients were treated in a year increased. On the other hand, the number of hospitals with a volume of >48 patients per year was stable. Because a relationship between provider volume and outcomes following oncological procedures was shown, a careful evaluation of the effectiveness of permanent implant brachytherapy for prostate cancer is needed. (*Cancer Sci*, doi: 10.1111/cas.12168, 2013)

When a medical technology, the usefulness of which has been established, is adopted in a country, how does the technology diffuse into medical practice? The speed and degrees of the diffusion depend upon many factors: consumer demand, promotional efforts of technology manufacturers, medical education, health insurance and payment systems, and governmental regulatory policies.[1]

Permanent implant brachytherapy for prostate cancer using iodine-125 (I-125) seeds was adopted in Japan in 2003.[2] The advantages of brachytherapy had been well recognized,[3] and the expectation for treatment was very high among Japanese urologists and radiation oncologists. In addition, the Cancer Control Act was approved in June 2006. Based on this law, the Basic Plan to Promote Cancer Control Programs was approved. One of its basic concepts is the equalization of cancer medical services including radiation therapy. This basic plan has stimulated the installation of new radiation therapy equipment at core hospitals.

In this study, we report on the diffusion pattern of permanent implant brachytherapy for prostate cancer in Japan since 2003, focusing in particular on the changes in the annual numbers of patients treated by brachytherapy per hospital since 2003.

Materials and Methods

We examined the annual numbers of prostate cancer patients per hospital in Japan, who were treated with I-125 seed implant brachytherapy with or without external beam radiation therapy. The use of palladium-103 (Pd-103) seeds, which is common in the United States, is not permitted in Japan. To elucidate the actual number of patients treated in a year, the hospitals were excluded from the count if brachytherapy was begun in a hospital within the given year, and thus was only available for part of the year. Because brachytherapy using I-125 seeds was adopted in Japan in 2003, the annual numbers of patients treated with brachytherapy between 2004 and 2011 were examined. These data were estimated from the database by Japanese Prostate Permanent Seed Implantation Study Group.[4] In Japan, I-125 seeds are supplied from two radiation source supply companies to medical institutions via the Japan Radioisotope Association (JRIA). Their database was also used to confirm the estimation.

Results

The total estimated number of patients treated with brachytherapy at hospitals where more than 1 year had passed since brachytherapy was first made available is shown in Table 1. In 2004, 269 patients were treated by brachytherapy only in two hospitals. However, the numbers increased rapidly. A total of 1412 patients were treated at 23 hospitals in 2005, 2783 patients were treated at 83 hospitals in 2008, and 3793 patients were treated at 109 hospitals in 2011.

Figure 1 shows the number of patients treated per hospital in 2005, 2008, and 2011. The mean/median number of patients treated per hospital was 61.4/42 in 2005, 33.5/25 in 2008, and 35.0/24 in 2011. Almost half of the patients in Japan were treated at the top six hospitals in 2005, at the top 18 hospitals in 2008, and at the top 22 hospitals in 2011. The number of hospitals in which 24 or fewer patients were treated in a year (i.e., two patients per month) was four in 2005, 40 in 2008, and 60 in 2011.

Figure 2 shows the distribution of the annual number of patients treated with brachytherapy per hospital from 2004 to 2011. The percentage of hospitals is also shown according to the number of patients per year in Table 1. The number of hospitals where 24 or fewer patients were treated in a year increased rapidly, in particular after 2006. On the other hand, the number of hospitals with a volume of >48 patients per year was stable.

Discussion

Although the advantages of brachytherapy were well recognized among Japanese urologists and radiation oncologists, low dose rate brachytherapy for prostate cancer using I-125 or Pd-103 seeds had not been allowed in Japan, because of the

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Table 1. Total number of hospitals/patients and the breakdown of hospitals according to the number of patients per year, among hospitals where more than 1 year has passed since brachytherapy was first made available

	2004	2005	2006	2007	2008	2009	2010	2011
Total number of hospitals	2	23	38	60	83	94	102	109
Estimated total number of patients	269	1412	1795	2516	2783	3112	3442	3793
Percentage of hospitals								
>96 patients/year	50.0	17.4	7.9	5.0	4.8	7.4	6.9	6.4
48–96 patients/year	50.0	30.4	28.9	23.3	10.8	10.6	11.8	11.9
24–48 patients/year	0.0	34.8	36.8	35.0	36.1	31.9	24.5	26.6
12–24 patients/year	0.0	17.4	10.5	18.3	32.5	28.7	35.3	33.9
≤ 12 patients/year	0.0	0.0	15.8	18.3	15.7	21.3	21.6	21.1

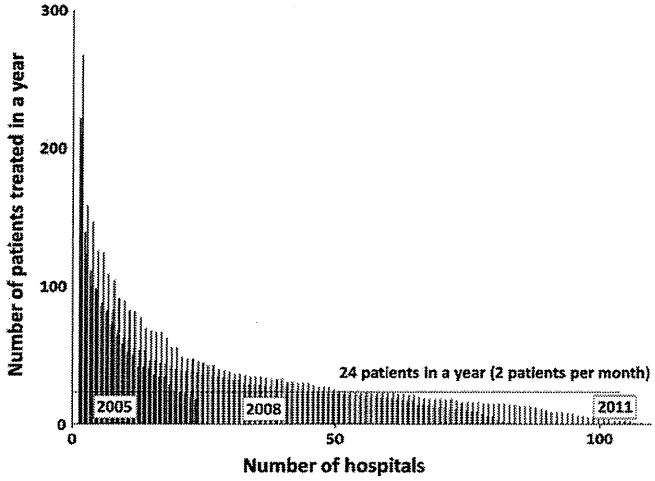

Fig. 1. The annual number of patients treated with brachytherapy per hospital in hospitals where more than 1 year had passed since brachytherapy was first made available, in 2005, 2008, and 2011.

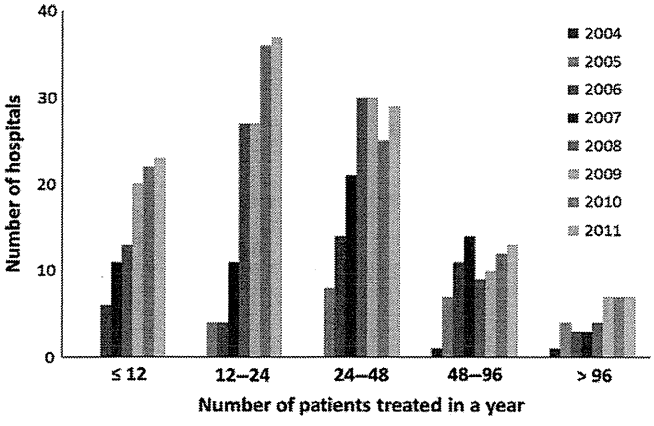

Fig. 2. Distribution of the annual number of patients treated with brachytherapy per hospital from 2004 to 2011.

strict Japanese laws on radiation safety.[2] However, after long discussions between members of the Japanese Society for Therapeutic Radiology and Oncology (JASTRO), the Japanese Urological Association (JUA), the Ministry of Health, Labor, and Welfare, and the Ministry of Education and Science, permanent implant brachytherapy for prostate cancer using I-125 seeds was approved in July 2003.[2] Even after permanent implant brachytherapy was permitted in Japan, only a limited number of institutions started the treatment, in part because of the very low price fixed by the Japanese health insurance system.[2] However, after a higher price for brachytherapy was approved by the Japanese health insurance system in April 2006, many institutes started providing the treatment, as shown in Figures 1 and 2. In particular, the number of hospitals with a low volume of patients increased.

Oncological procedures may have better outcomes if performed by high-volume providers. Killeen *et al.*[5] revealed that high-volume providers have significantly better outcomes for complex cancer surgery, in particular for pancreatectomy, esphagectomy, gastrectomy and rectal resection. In Japan, influences of hospital procedure volume on cancer survival have been under intense investigation using The Osaka Cancer Registry's data.[6–10] As for localized prostate cancer, Jeldres *et al.*[11] examined the effect of annual and cumulative provider volume on the rate of use of secondary therapies using a cohort of 3907 patients treated with definitive external-beam radiation therapy. They demonstrated lower rates of secondary therapy for providers with an annual provider volume >10 cases and for those with a cumulative provider volume >200 cases. Taussky *et al.*[12] showed that seed migration in prostate brachytherapy depended on experience and technique. Chen *et al.*[13] concluded that patients treated with brachytherapy by higher-volume physicians were at lower risk for recurrence and prostate cancer death. Interestingly, they showed that there was no significant association between hospital volume and recurrence, prostate cancer death or all deaths.

Japanese urologists and radiation oncologists have made a great effort to maintain the safety and quality of permanent implant brachytherapy for prostate cancer. JASTRO, JUA, and the Japan Radiological Society (JRS) have published guidelines for brachytherapy (in Japanese).[2,14] These guidelines require physicians involved in this treatment to attend an education course held by JRIA. The guidelines also strongly recommend that each institution administering this treatment should have a urologist certified by the JUA and a radiation oncologist certified by JASTRO and/or JRS in full-time employment.[2] In addition, training workshops have been held at regular intervals to maintain or improve the technical level of permanent implant brachytherapy for prostate cancer. It is not still clear whether the provider volume is associated with outcomes following brachytherapy for prostate cancer in Japan.

The diffusion of a new medical technique depends upon many factors including consumer demand and health insurance and payment systems.[1] In Japan, although health care is under the management of an obligatory insurance system, it is within the framework of a capitalist economy.[15] Given this situation, a new "Basic Plan to Promote Cancer Control Programs" was

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approved in 2012. In addition to the further promotion of radiation therapy and the training of doctors/staff members specializing in this area, the plan recommends the centralization of high-precision radiation therapy including intensity-modulated radiation therapy (IMRT) in each medical region.

There are several new options for patients with clinically localized prostate cancer including robotic surgery, brachytherapy, and IMRT. The majority of the published papers have shown similar treatment results in large-scale institutions. However, after the diffusion of a new medical technique, evaluation of the quality remains an important issue. Therefore, a nationwide multi-institutional cohort survey for prostate brachytherapy focusing on the effect of provider volume on treatment efficacy and safety is needed.

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Disclosure Statement

The authors have no conflict of interest.

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IMRT/ブラキセラピーの登場による前立腺癌治療方針のパラダイムシフト

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■ はじめに

前立腺癌に対する放射線治療は，コンピュータ技術の発達とともに近年急速に進歩している。本邦においても，三次元原体放射線治療（three-dimensional conformal radiotherapy：3D CRT），強度変調放射線治療（intensity-modulated radiotherapy：IMRT），画像誘導放射線治療（image-guided radiotherapy：IGRT）などの最新の技術が多くの施設に導入され，普及期を迎えている。また，2003年にヨウ素125密封小線源永久挿入療法（ブラキセラピー）が本邦でも使用可能となり，急速に全国へ普及した。前立腺に対する線量増加の有用性に関する臨床試験の結果が次々と明らかとなり，臨床現場へフィードバックされることにより，前立腺癌に対する放射線治療の照射法，線量等は急速に変化しつつある。これらの導入により大きなパラダイムシフト（PS）が起こりつつある。

本項では，高精度放射線技術およびブラキセラピーの導入により，前立腺癌放射線治療がどのように変化し，将来どのように変化していこうとしているかについて考察する。

❶ 前立腺癌の治療方針のPSへのIMRTの役割は？

1）線量増加

前立腺癌の外部照射におけるIMRTの重要性は明らかである。すなわち，IMRTを実施することによって，直腸の線量を低減することができ，有害事象の頻度を低下させることができる。それゆえに，安全に前立腺への投与線量を増加することが可能となる。前立腺癌は投与線量が大きいほどPSA非再発率が向上することが知られているため[1]，IMRTを実施することにより，有害事象を増加させることなくPSA非再発率を向上させることが可能となる。

これらのエビデンスの蓄積をふまえ，米国のNCCN（National Comprehensive Cancer Network）guidelineでは，2005年の時点で低リスクでは70～75 Gyが，中および高リスクについては75～80 GyがPSA非再発率を向上させるらしい（appear to be appropriate）と婉曲的な表現が用いられていた。しかし，2013年では低リスク群では75.6～79.2 Gy，中および高リスク群では最大81 Gyまでの線量増加によりPSA非再発率の改善が得られる（are appropriate）と断定的な表現が用いられており[2]，IMRTやIGRTなどを併用して，高線量を投与することがすでに標準となっている。

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〔索引用語：前立腺癌，IMRT，ブラキセラピー〕

2) 本邦の現状

コンピュータ技術が飛躍的に発展する以前は，直腸などの重要臓器に対する線量低減は，矩形の照射野に置かれた鉛ブロックで行われていたため，どうしても正常組織の線量を低減することに限界があった。しかし，前述の様に，3D CRT，IMRT などの高精度放射線技術が開発されることにより，安全により多くの線量が投与されるようになり，それに伴い，前立腺への投与線量も増加してきている。本邦における放射線治療の実態調査は，厚生労働省の研究助成金による医療実態調査研究（Patterns of Care Study：PCS）にて実施されてきた。その調査によれば，照射線量の中央値は，65 Gy（1996～1998 年）から 70 Gy（2003～2005 年）と上昇しており，より高精度な照射方法の普及に伴い，経年的に高い線量が投与される傾向にあることを示している[3)4)]（図 1）。一方，米国での PCS 研究からの報告では，1999 年の時点ですでに前立腺への投与線量の中央値は 70 Gy を超えており[5)]，投与線量からみれば，本邦では米国と比べて数年の遅れがあった。しかし，2010 年に行われた全国アンケート調査では，3D CRT での線量の中央値は 70 Gy であったのに対して，IMRT での線量の中央値は 76 Gy であり，現在では IMRT を行う場合にはかなりの高線量が投与されているということがいえる[6)]。米国では 1 回 1.8 Gy が用いられることも多く，1 回 2 Gy が標準的に用いられる本邦との比較は慎重であるべきだが，もし仮に，前立腺癌の α/β 値が 1.5 と仮定すると，1 回 2 Gy での 76 Gy は，1 回 1.8 Gy での 80.6 Gy に相当し，本邦でも米国なみの線量増加がなされていると考えてよいであろう。

3) 有害事象

前立腺癌に対する外部照射では，線量増加によりどの程度有害事象が増加するのであろうか。Cahlon らのレビューによると[7)]，3D CRT では，70 Gy 程度の通常照射による消化器系の grade 2 以上の有害事象は 10～15%程度であるが，75～78 Gy まで線量増加を行うと 15～25%程度と増加する傾向にあることが報告されている。泌尿器系の有害事象についても，10～20%から 15～25%と同様な傾向にある。一方，IMRT にて線量増加を行う場合には，消化器系の有害事象は 3～10%程度と 3D CRT と比べて有害事象の頻度が有意に低下している報告が多い。興味深いことに，泌尿器系の有害事象の頻度は 3D CRT，IMRT のどちらで実施しても大きな差はなく，IMRT による低減効果はみられていない。一般的には IMRT を用いて線量増加を図った場合，消化器系の有害事象は低減できるが，泌尿器系の有害事象を低下させることは難しいと考えられている[7)]。このひとつの理由として，IMRT では明かに物理的に直腸線量を低減できるが，尿道などの線量低下は難しいことが挙げられる。これが通常の IMRT での線量増加の限界であろう。

❷ 前立腺癌の治療方針の PS への IGRT の役割は?

1) IGRT

放射線治療のターゲットとなる前立腺の位置は，毎回の治療ごとに変動することが知られている。前立腺の位置は，日々のセットアップエラーに加えて，直腸，膀胱容量などによっても影響される。さらに体位によっては前立腺の呼吸性移動も無視できなくなる。もし，この治療ごとの位置変動を小さくすることができれば，より小さい照射野で照射でき，有害事象を低減化できる可能性がある。

このような放射線治療時の不確定要素を低減するために，治療直前または治療中のターゲットの位置を確認して照射する，いわゆる画像誘導放射線治療（IGRT）が近年急速に普及してきた。IGRT の方法としては，金属マーカーを前立腺周囲に挿入し，治療直前に X 線透視等でマーカーの位置を確認する方法，治療装置に連携した超音波装置や CT 等により位置確認を行う方法などがある。

2010 年に実施された，本邦における IGRT，IMRT の実施状況に関するアンケート調査では，117 施設の回答のうち，71 施設にて IGRT が実施されていた[6)]。IGRT の方法は kVCT，MVCT，透視装置，超音波装置，金属マーカー等，様々な手法で行われていたが，前立腺癌の放射線治療では，前立腺または金属マーカーでの位置合わせが 37 施設（52.1%），骨情報での位置合わせが 33 施設（46.5%）であった。このうち，直腸側の PTV マージンでは，前立腺または金属マーカーでの位置合わせでは中央値 5mm（3

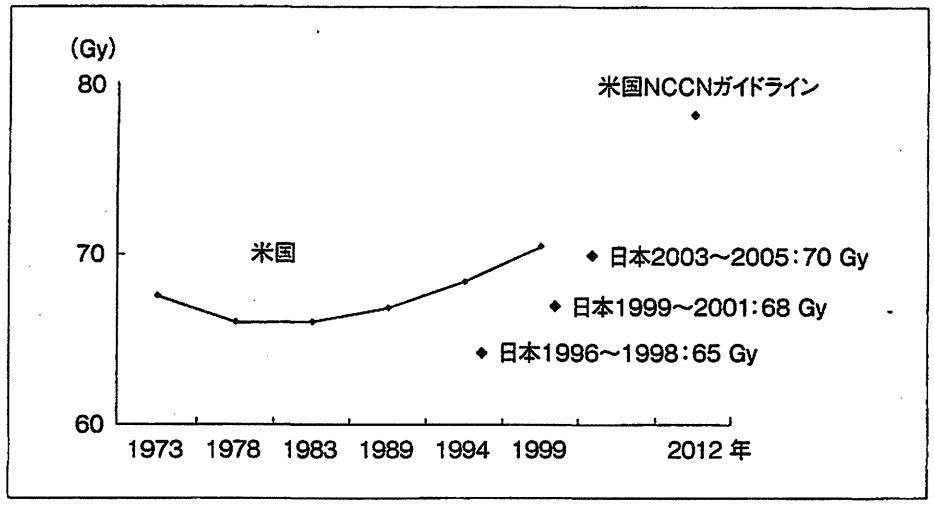

図1　前立腺癌への投与線量の年次的推移（米国および日本の医療実態調査研究の結果から）

～7mm），骨情報での位置合わせでは中央値6mm（3～10mm）と，前立腺または金属マーカーでの位置合わせで小さい傾向にあった。

このように，前立腺癌の外部照射にてIGRTを実施することにより，より小さい照射野を用いることができ，それによって有害事象を低減化できる可能性がある。

2）寡分割

上述のように，IGRTを実施することのメリットのひとつは，毎回の治療ごとのセットアップエラー等による位置変動を小さくすることにより，照射野を縮小でき，有害事象低減に貢献することである。もちろん，照射野を縮小できる分，投与線量を増加させることも可能である。しかし，IMRTだけでもgrade 2以上の消化器系の有害事象は3～10%程度で，grade 3以上では1%以下である。一方，IMRTやIGRTを利用して直腸側のマージンを縮小したからといって，尿道の線量を低減することは難しく，泌尿器系の有害事象の発生頻度を改善することは困難であろう。

実は，IGRTのもうひとつの利点として，1回線量を増加させ，治療回数を減らす（寡分割照射，hypofractionation）ことにより治療成績向上につながる可能性が指摘されている。

放射線に対する感受性の指標としてα/β比が知られており，通常の悪性腫瘍は10程度，直腸などの正常組織では2～3程度とされている。通常の腫瘍に対する放射線治療では，1回線量を大きくすると，α/β比の小さい正常組織の有害事象の可能性が高くなり，腫瘍のコントロール率向上のメリットよりもマイナス面のほうが大きいとされている。よって歴史的には1回線量を1.8～2 Gyとし，総線量60～70 Gyを照射するスケジュールが選択されてきた。しかし，前立腺癌細胞は増殖速度が遅いため，前立腺癌のα/β比は通常の腫瘍に比べて非常に小さいと推測されている[8]。もしこの予想が正しく，前立腺癌のα/β比が直腸や尿道などよりも小さいのであれば，1回線量をより大きくし，分割回数を少なくすればするほど治療可能比が高くなることが推測される。たとえば，正常組織のα/β比を3と仮定し，前立腺癌のα/β比が1.5であるとすれば，1回2 Gy，総線量70 Gyでの有害事象が起こる確率は，1回7 Gyでの総線量35 Gyと同等と推定されるが，1回7 Gy，総線量35 Gyの前立腺癌に対する治療効果は，2 Gyでの85 Gy程度に相当すると計算できる。すなわち，1回線量を増加させることにより，有害事象の危険性は増加させずに，治療効果のみを高めることが可能となるのである。

しかし，ここで問題となるのが，位置精度である。通常分割での前立腺癌に対する照射回数は37～40回程度であり，セットアップエラー，呼吸性移動や直腸容積などによる前立腺位置の変動があっても，多数回の照射により平均化されるため，それほど治療成績に影響しない。しかし，照射野のマージンが小さい

場合，1回線量をより大きくし，分割回数を小さくすればするほど，前立腺の位置の不確定要素が治療成績に大きく関係してくるようになる[9]。すなわち，前立腺の位置の不確定要素を解決しない限り，回数を減らすことによってかえって治療成績が低下する危険性がある。よって，毎回の前立腺の位置の不確定要素を低減させるIGRTを用いてこそ，寡分割照射を安全にかつ効果的に実現できると考えられている。

前立腺癌に対する寡分割照射についての後ろ向きの報告は数多くなされている。Kupelianらは，超音波装置を使ったIGRTにて前立腺の位置を同定し，IMRTにて1回2.5 Gy，total 70 Gyを照射した770例についての後ろ向きの治療成績を報告している[10]。5年PSA無再発率は82%と良好であり，grade 2以上の直腸障害，尿路系障害はそれぞれ4.5%，5.2%と通常分割法と同程度であったとしている。

現在，寡分割照射の有効性を確認するために，IGRT，IMRTを使った寡分割照射の臨床試験が数多く実施されている[11]。

本邦でも，厚生労働科学研究費補助金がん臨床研究事業「放射線治療期間の短縮による治療法の有効性と安全性に関する研究」の援助により，前立腺癌に対するIMRT/IGRT併用寡分割照射法の第Ⅱ相臨床試験が開始されている。これは，前立腺癌に対して前立腺合わせでのIGRTを用いて，IMRTによる少数分割法70 Gy/28回（1回2.5 Gy）が有効かつ安全であるかを探索的に検討する試験であり，Primary endpointを5年遅発性有害事象発生割合としている。対象は低・中リスク（T1-2c and PSA =< 20 and G =< 7）または高リスク因子で危険因子（T3a，20 < PSA =< 30，G = 8，9）がひとつのみの症例で，2012年6月より症例登録が開始されている。これらの結果次第によっては，寡分割照射がスタンダードのひとつとなる可能性を秘めている。

また，前立腺癌に定位的に放射線治療を行い，さらに少ない回数で，1回大線量を投与する試みもある。Katzらは，前立腺癌304例（低リスク211例，中リスク81例，高リスク12例）に対して，サイバーナイフにより定位的に35～36.5 Gy/5分割を照射し，5年PSA無再発率は低リスク97%，中リスク90.7%，高リスク74.1%と良好な治療成績であったと報告している[12]。サイバーナイフでは，さらに尿道の線量も低減することができ，高線量率組織内照射のような線量分布を形成できることが特徴である。このような大線量，少数分割はいまだ研究的な治療法であるが，欧米を中心に臨床試験が進行している。

❸ 前立腺癌の治療方針のPSへのブラキセラピーの役割は?

前立腺癌に対する低線量率線源を用いた密封小線源永久挿入療法（ブラキセラピー）は，欧米では古くから実施されていたが，ようやく本邦でも2003年にヨウ素125による治療が可能となった。2006年により保険収載されてからは急速に全国へ普及している。従来，ブラキセラピーは，低リスクおよび中リスク前立腺癌が主な適応であり，一般的には高リスク前立腺癌は適応とはなっていなかった。前述のNCCN guidelineによれば，2004年では低リスクにはブラキセラピー単独，中リスクにはブラキセラピーと外部照射40～50 Gyが推奨され，高リスクはブラキセラピーには適さない（are poor candicates）とされていた。しかし，2007年には，高リスクの一部の患者には外部照射とホルモン療法とを併用することによって効果的かもしれない（it may be effective）との表現に変わり，2013年では，高リスク例は，ブラキセラピーと外部照射40～50 Gy，ホルモン療法にて治療されるかもしれない（may be treated）との表現になっている[2]。

このように，ガイドラインが変化してきたのは，高リスク前立腺癌でも十分な高線量を投与すればPSA非再発率の改善が期待できるエビデンスが蓄積されてきたからである。Grimmらは，過去に報告された，前立腺癌に対する手術，外部照射，ブラキテラピーの膨大な論文を調査し，高リスク前立腺癌においても，ブラキテラピー＋外部照射±ホルモン療法が，手術，ブラキテラピー，外部照射単独と比較して，優れている傾向にあったことを報告している[13]。

本邦も，高リスク前立腺癌に対してブラキテラピーにて治療される症例は増加しており，また，高リスク前立腺癌に対する小線源・外照射併用放射線療法における補助ホルモン治療の有効性に関する臨床研究（TRIP試験）も進行している。この試験結果が明

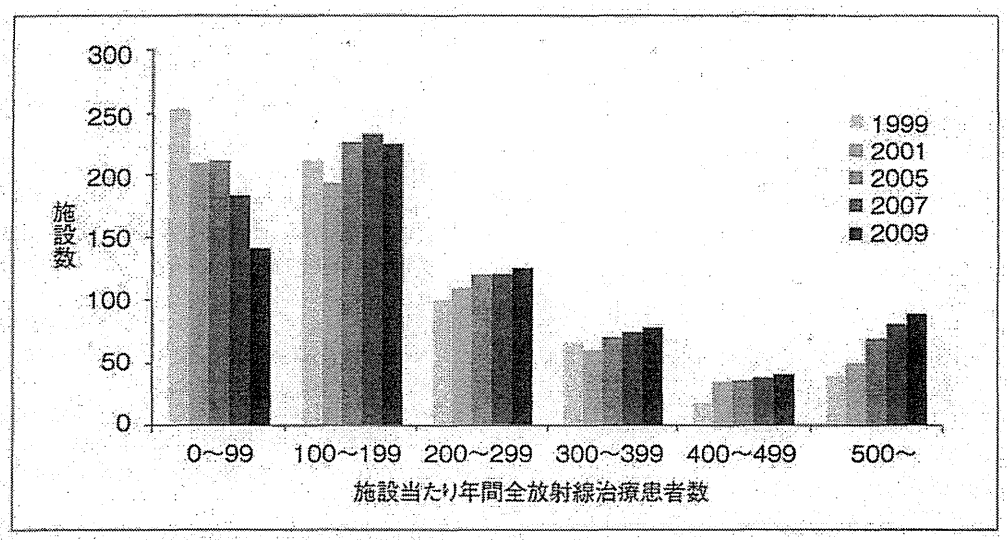

図2　施設当たり年間全放射線治療患者数の推移

かとなれば，高リスク前立腺癌に対するブラキテラピーの有用性が確立するであろう。

❹ 高精度放射線治療やブラキテラピーの普及と質の担保への課題

前立腺癌のブラキテラピーに関しては，2003年に治療が開始されて以来，一施設当たりの年間治療数がどのように変化しているかの調査が施行されている[14]。治療を開始してから1年以上が経過した施設数は，2004年ではわずか2施設で計269例が治療されていたが，2005年には23施設で1,412例が治療され，2008年には83施設で2,783例，2011年には109施設で3,793例が治療されていた。しかし，一施設当たりの年間治療患者数の中央値は2005年では42例，2008年では25例，2011例では24例と年々低下し，特に年間治療数が24例以下（月2例以下），12例以下（月1例以下）の施設は急増していたが，年間48例以上を治療する施設数は大きな変化はなかった[14]。一般的に悪性腫瘍の治療においては年間治療数と治療成績との相関があるとの報告もある[15]。しかし，日本泌尿器科学会，日本放射線腫瘍学会の協力のもと，安全講習会，技術講習会などが数多く行われ，その臨床的質を保つ多大な努力が払われており，本邦での前立腺癌のブラキテラピーに関しては，年間治療数と治療成績との相関関係ははっきりとは証明されていない。

一方，前立腺癌の外部照射では，詳細なデータについて報告されたものはない。そこで，日本放射線腫瘍学会から定期的に公表されている構造調査から，各年ごとの一施設当たり年間全放射線治療患者数の推移を求めて示したものが図2である。前立腺癌の治療数は不明であるため，単に全放射線治療患者数をみたものではあるが，1999～2009年までに治療数が年間100例に満たない施設数は減少している一方，年間500例以上を治療している施設数は増加している。しかし，これらの施設におけるIMRTなどの高精度放射線治療がどのように実施されているかなどについての質的な評価は今後正しくなされていくべきであろう。

■ おわりに

これまで述べてきたように，外部照射については，線量増加そして寡分割照射へ，ブラキテラピーについては高リスクへの適応拡大へと大きなPSが起きている。今後はさらに陽子線治療，炭素線治療などの粒子線治療が加わってくる。

2007年に定められたがん対策基本計画では，癌医療の均てん化の促進がうたわれ，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の方向性が定められた。2012年度にはその見直しが行わ

れ，放射線療法の質を確保し，地域格差を是正し均てん化を図るとともに，人員不足を解消する取組に加えて，一部の疾患や強度変調放射線治療などの治療技術の地域での集約化を図る，とされた。今後は単に，高精度放射線治療が実施できるというだけではなく，高い質を保つために，集約化も含めた放射線治療の効率化を模索していく必要があろう。

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Summary

A paradigm shift in radiation treatment strategy for prostate cancer by intensity-modulated radiotherapy and brachytherapy

A paradigm shift in radiation treatment strategy for prostate cancer has been stimulated by precise radiotherapy including intensity-modulated radiotherapy (IMRT) and brachytherapy. Using IMRT technique, dose escalation has been achieved without increasing late gastrointestinal toxicities. Hypofractionation treatment protocols for prostate cancer with IMRT and image-guided radiotherapy may have a therapeutic advantage. Low dose rate brachytherapy may offer a better outcome for high-risk prostate cancer. However, in addition to the introduction of new technologies, it is also important to evaluate the quality of new treatment techniques in each institution.

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CLINICAL STUDY

Risk factors for early death after surgery in patients with brain metastases: reevaluation of the indications for and role of surgery

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Abstract Surgical resection remains an important option for the treatment of brain metastases despite recent advancements in radiotherapy and systemic therapy. When selecting surgical candidates, it is important to exclude terminal cases who will receive neither a survival benefit nor an improvement in their quality of life. We reviewed a total of 264 surgical cases of brain metastases and analyzed the clinical characteristics of early death in order to clarify the indication for and the role of surgery. The median survival time (MST) after surgery in all cases was 12.4 months. Early death was defined as death within 6 months, and 23 % (62 cases) of this series were succumbed to this. A decrease in postoperative Karnofsky performance status (KPS) (<70) ($P = 0.041$), lack of systemic therapy after surgery ($P < 0.0001$), and uncontrolled extracranial malignancies ($P = 0.0022$) were significantly related to early death in multivariate analysis, while preoperative KPS (<70) and recursive partitioning analysis (RPA) class were related to early death only in univariate analysis ($P < 0.05$). When analyzing patients with uncontrolled extracranial malignancies and those with a postoperative KPS score of 70 or greater (who were generally candidates for systemic therapy), the MST was significantly longer in the systemic therapy (+) group compared with the systemic therapy (−) group (12.5 vs. 5.6 months; $P = 0.0026$). Our data indicate that the postoperative RPA class and treatment strategy were associated with early death. Deterioration of patients by surgery should be avoided in the treatment of brain metastases.

Keywords Brain metastases · Surgery · Early death · Leptomeningeal metastases

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Introduction

Brain metastasis is a life-threatening event for cancer patients and indicates that cancer has reached the advanced stages. Surgical resection remains an important option for treatment despite recent advancements in radiotherapy and chemotherapy. The aims of surgical resection are mass reduction and rapid improvement of neurological status.

Knowledge regarding the prognosis of extracranial lesions is important when making decisions about surgery. Several studies have attempted to identify prognostic factors, and various classification systems including recursive partitioning analysis (RPA) classification and graded prognostic assessment (GPA) have been developed [1, 2]. These classification systems have mainly been validated in patient populations treated with radiotherapy; however, some reports have indicated that these systems are useful for predicting survival time after surgery [3–9]. Considering the risks associated with treatment, terminal cases who receive neither a survival benefit nor an improvement in their quality of life (QOL) should be excluded during the selection of surgical candidates.

Herein, we describe a retrospective analysis of the relationship between clinical characteristics and the

outcome of surgery for brain metastases, and we discuss the indications for and the role of surgery.

Materials and methods

Patients

In total, we included 264 cases (156 men and 108 women) who underwent resection as their first surgery for brain metastases at the National Cancer Center Hospital in Japan between January 2000 and December 2011. The mean age of the included patients was 57.5 years (range 19–87), and their clinical characteristics were extracted from their medical records. Overall survival was calculated from the first resection surgery to death. The Karnofsky performance status (KPS) was determined as recorded or was retrospectively estimated from information obtained from the clinical chart by three neurosurgeons (Y.N., Y.M., and S.S.) who performed surgery on the patients. RPA classification of each patient was performed using published criteria [1]. Preoperative status, including performance status and RPA, was evaluated at the time of surgery, while postoperative status was evaluated approximately 1 month after surgery. The performance status and RPA class of patients who died within 1 month after surgery were recorded as 0 and III, respectively. Information regarding the RPA class and status of extracranial malignancy was not available for 1 case.

The cause of death was determined by clinical evaluation. Neurological deaths were defined as cases with neurological deterioration and stable extracranial disease as well as cases with apparent fatal progression of intracranial lesions or leptomeningeal metastases (LMM) regardless of systemic conditions.

The analysis in this study was approved by the local institutional review board (reference no. NCC16-066).

Treatment

Our basic surgical indications for brain metastases were described in a previous report [10]. Surgical candidates included patients with the following characteristics: (1) a post-surgery life expectancy of 6 months or more based on information from medical oncologists, (2) no clinical symptoms or apparent radiological findings indicating LMM, and (3) single metastases measuring $\geqq 3$ cm, or multiple or smaller tumors associated with severe neurological symptoms such as cerebellar metastases. In principle, adjuvant radiotherapy usually began 8 days after surgery. Adjuvant stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) was undergone only for the treatment of the surgical remnant or unresected lesion(s) in patients with multiple metastases. After brain metastases were controlled, patients received further systemic therapy or best supportive care (BSC) according to decisions made by medical oncologists.

A total of 37 patients received RT prior to surgery. In patients who experienced tumor recurrence after radiotherapy, surgical indication was judged via discussion with senior radiologists.

Early death

Early death was defined as death within 6 months after the first surgery for brain metastases, and the clinical profiles between the early death group and the non-early death group were compared. This definition is based on a comparison between the outcome of whole brain radiation therapy (WBRT) and surgery. The median survival time (MST) after WBRT alone is approximately 6 months [11–13]; therefore, if surgery confers a survival benefit, it should extend this time period.

Statistical analysis

Statistical analysis was performed using JMP version 10 (SAS Institute, Cary, NC, USA). The data for survival time were analyzed using the Kaplan–Meier method. A P value below 0.05 was considered statistically significant.

Results

Analysis for all cases

When all cases were analyzed, the median follow-up, MST, 1-year overall survival rate, and 5-year overall survival rate were 11.2, 12.4 months, 52, and 12 %, respectively. The 3 and 6-month overall survival rates were 89 and 75 %, respectively. When patients were divided according to preoperative RPA class, we determined that MST was 21.8 months for class I (59 cases, 22 %), 12.4 months for class II (148 cases, 56 %), and 6.5 months for class III (56 cases, 21 %) (Fig. 1a). When we reevaluated the data using postoperative RPA classification, MST was 20.8 months for class I (66 cases, 25 %), 11.2 months for class II (176 cases, 67 %), and 4.3 months for class III (21 cases, 8 %) (Fig. 1b). Both of pre- and postoperative RPA class were significantly related with survival ($P < 0.0001$, log-rank test). The relationships between preoperative and postoperative RPA class are shown in Supplementary Table 1.

KPS improved in 53 %, was unchanged in 40 %, and worsened in 7 % of all cases after surgery. Surgical complications were observed in 20 cases (7.6 %) including 8 instances of neurological deterioration due to surgical