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ORIGINAL ARTICLE

PROSPECTIVE TRIAL OF CHEMOTHERAPY-ENHANCED ACCELERATED RADIOTHERAPY FOR LARYNX PRESERVATION IN PATIENTS WITH INTERMEDIATE-VOLUME HYPOPHARYNGEAL CANCER

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Abstract: *Background.* Altered fractionation radiotherapy (RT) improves locoregional control in head and neck cancer without aggravation of late adverse events. To improve successful larynx-preservation rates in patients with resectable, intermediate-volume hypopharyngeal cancer, a prospective trial of chemotherapy-enhanced accelerated RT was conducted.

Methods. Patients with T2 to T4 hypopharyngeal cancer received 40 Gray (Gy)/4 weeks to the entire neck followed by boost RT administering 30 Gy/2 weeks (1.5 Gy twice-daily fractionation). Cisplatin and 5-fluorouracil were administered concomitantly only during boost RT.

Results. Thirty-five patients were enrolled in this study. All patients completed this protocol as planned. After a median follow-up period for surviving patients of 59 months (24–90 months), overall survival and local control rates at 3 years were 91% (95% confidence interval, 81% to 100%), and 88% (79% to 99%), respectively. All surviving patients maintained normalcy of diets.

Conclusion. This regimen was feasible with encouraging oncological and functional outcomes. © 2011 Wiley Periodicals, Inc. *Head Neck* **00:** 000–000, 2011

Keywords: hypopharyngeal cancer; accelerated fractionation radiotherapy; chemotherapy; larynx preservation; long-term swallowing function

Approximately one fourth of oral cavity or pharyngeal cancers in Japan originate from the hypopharynx, and the estimated incidence of patients with hypopharyngeal cancer is about 2500 per year.[1,2] Larynx-preserving approaches for hypopharyngeal cancer showed no obvious difference in overall survival compared to other surgical approaches in a randomized study[3] as well as in a large population-based study.[4] Conventional fractionation radiotherapy (RT) alone for patients with early-stage hypopharyngeal cancer with T2 disease achieved a local control rate of approximately 60%.[5,6] RT alone using altered fractionation significantly improved local control rates without deterioration of serious late adverse events.[7,8] This approach could achieve favorable larynx-preservation rates in selected patients with hypopharyngeal cancer with low-volume, T1 or T2 primary tumors which had tumor volumes of 7 mL or smaller.[9,10] However, less favorable results were expected for other patients with larger hypopharyngeal cancers that required total laryngectomy.[10,11] Therefore, the combination of chemotherapy with RT is required to improve larynx-preservation rates in these patients.[12]

Because hypopharyngeal cancer originates from the narrowest part of the upper digestive tract, late dysphagia and aspiration due to consequential late effects are not uncommon even after successful eradication of the disease after intensive chemoradiotherapy (CRT).[13–16] Therefore, special attention should be paid to minimize severity and duration of serious mucosal toxicity by a deliberate combination of altered fractionation RT and/or chemotherapy with meticulous patient selection according to the morphology and volume of the primary tumor.[10,17]

High incidence of distant metastasis in patients with hypopharyngeal cancer was mainly because of the high frequency of advanced nodal disease at the time of initial presentation.[18] If a patient has an intermediate-volume tumor without advanced nodal metastasis, tumor control above the clavicle instead of prevention of systemic tumor dissemination should be prioritized. We previously reported a favorable local cure rate after conventional fractionation RT in patients with intermediate-volume disease at the pharyngolarynx; however, further improvement of

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local control with good function is needed.[19] This study was based on the principle that use of chemotherapy as a radiation sensitizer should not compromise the benefit of altered fractionation RT alone in terms of long-term swallowing function in these patients.[7,8] Accelerated fractionation that delivers dose-dense RT during the latter part of the entire treatment is a reasonable strategy to overcome accelerated repopulation of the tumor, which is supposed to begin at approximately 4 weeks after commencement of RT.[8,20,21] The aim was to enhance the effect of treatment using both twice-daily RT and chemotherapy only during the period when acceleration of tumor repopulation is to be expected. Although the incidence of these patients was expected to be limited, and the true efficacy should be tested in multiinstitutional collaborative studies, preliminary results of this "chemotherapy-enhanced" accelerated fractionation RT were promising.[22] Therefore, matured results of a prospective, single institutional trial were reported here to demonstrate the safety and validity of conducting a larger trial of this regimen.

MATERIALS AND METHODS

Patient Population. Patients were required to have previously untreated, histologically proven squamous cell carcinoma of the hypopharynx that was judged amenable to margin-free resection with total laryngopharyngectomy and neck dissection by expert head and neck surgeons in our institution. Those who were considered as candidates for partial laryngectomy or who had T1 disease were ineligible for this study. In addition, the following eligibility criterion were required: age ranging from 20 to 75 years; no bilateral lymph node metastasis on CT and/or MRI scans; no evidence of distant organ metastasis (clinically M0); Zubrod Performance Status (PS) of 0 to 2; no history of RT for the head and neck area; adequate bone marrow and organ function; no history of other malignancies within 5 years before enrollment; and no history of ischemic heart disease and/or symptomatic cerebrovascular accident within 3 months before enrollment. Patients who had simultaneous superficial esophageal and/or gastric cancers that were judged amenable to margin-free resection using endoscopic mucosal resections were eligible for the study. All patients provided written informed consent. We received approval for this study from our institutional ethics committee.

Pretreatment Evaluation. Disease was staged according to the American Joint Committee on Cancer Staging Manual (6th edition). Staging procedures consisted of physical examination, head and neck fiberscope, CT and/or MRI of the head and neck region, chest X-ray, upper abdominal ultrasound, and gastroesophageal endoscopy. CT of the chest and bone scans were performed as indicated. Laboratory studies included a complete blood cell count, routine liver and kidney function tests, and electrocardiography. All patients underwent pretreatment dental examinations, and dental therapy was done as indicated before the start of RT. Nutritional support by using a nasogastric tube or percutaneous gastrostomy was not done in this protocol.

Radiotherapy. A total dose of 40 Gray (Gy)/4 weeks using 2 Gy once-daily fractionation was administered to the primary tumor, bilateral level II to IV lymph node stations, and retropharyngeal lymph nodes according to the American Joint Committee on Cancer Staging Manual (6th edition). This was followed by boost RT administering 30 Gy/2 weeks (1.5 Gy twice-daily fractionation) to the primary tumor with 2-cm margins. Interfraction interval was set as $\geq$6 hours. Maximum efforts were taken, if appropriate, to exclude the base of tongue and cervical esophagus at >2 cm below the caudal edge of the cricoid cartilage from irradiated volume of the boost RT. If a patient had gross nodal disease extending above the posterior belly of the subdigastric muscle and/or to level IV, which necessitated a larger irradiated volume than that described above during boost RT, neck dissection was performed before the start of RT. This was followed by a total of 55 Gy of RT that was administered to the surgical bed of this up-front nodal dissection, followed by additional 15 Gy to the primary tumor. Maximum dose to the spinal cord was restricted to 46 Gy/24 fractions. RT was delivered using 6 MV X-rays in all patients with 3-dimensional RT planning. Intensity-modulated radiotherapy was not used in this group of patients.

Chemotherapy. A single course of chemotherapy was concomitantly administered during the boost RT in expectation of a radiosensitizing effect.[23,24] Cisplatin 80 mg/m^2 was administered with intravenous hydration on the first day of chemotherapy, and 4-day continuous infusion of 5-fluorouracil 400 mg/m^2/day was started on the same day. Patients were hospitalized during the course of chemotherapy and received hydration and antiemetic therapy as indicated.

Dose Modifications. Grade 4 hematological toxicity or grade $\geq$3 dysphagia and/or swallowing pain required treatment break until these toxicities became grade $\leq$2. Chemotherapy was started only when the following criterion were fulfilled: white blood cell count $\geq$2000/mm^3, hemoglobin level $\geq$8.0 g/dL, platelet count $\geq$100,000/mm^3, any gastrointestinal toxicities of less than grade 3, serum bilirubin level $\leq$1.5 mg/dL, serum creatinine level $\leq$1.5 mg/dL, and dermal toxicity of less than grade 2. If patients did not meet these criterion, chemotherapy was postponed without RT break and administered only when patients satisfied the criterion within 7 days.

Outcome Measures and Statistical Considerations. Low accrual rate was expected in a single institutional setting, and experience of administering altered fractionation RT for hypopharyngeal cancer was limited in Japan at the time of protocol development.[6] Therefore, this trial was conducted as a feasibility study to plan a multiinstitutional trial of this regimen to evaluate the true efficacy with a sufficient number of patients. The primary endpoint was completeness of the protocol treatment without unplanned treatment break or dose modification. This trial used a 2-stage design wherein the expected rate of completeness was defined as 80%. This was tested against the threshold rate of 60% or lower with an alpha level of 5% and a power of 80%, which required an initial enrollment of 13 patients. If <8 of these 13 patients completed the protocol without unplanned break and dose modifications, the trial would be stopped. Otherwise, enrollment would be extended to 35 patients and the rate of completeness determined. Secondary endpoints were local control rate, progression-free survival, overall survival, and adverse events. Follow-up visits were requested monthly within 2 years after completion of RT, at least once per 3 months during the third year, and once per 6 months thereafter. Radiological examinations including CT and/or MRI of the head and neck were done at least twice within 6 months immediately after treatment, and at regular intervals of 6 to 12 months thereafter. Positron-emission tomography was not routinely done in this protocol. Time-to-event analyses from the start of RT were done using Kaplan–Meier estimates. Biopsy-proven recurrence of the primary tumor was considered as an event for calculating the local control rate, and patients who died without this event were censored at the time of last follow-up examinations. Death of any cause was defined as events in calculating overall survival. Also, recurrence at any site or death of any cause was used in estimating progression-free survival. Adverse events were estimated according to the National Cancer Institute Common Toxicity Criteria, version 2.0, and Radiotherapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Scheme.

Although not required in the protocol, volumetry of the primary tumor was estimated from CT scans during RT planning in all patients retrospectively using RT planning software (Xio, version 4.4, Elekta CMS Software, St. Louis, MO) by the principal investigator (M.K.).

RESULTS

Patients. Between October 2002 and March 2008, 35 patients were enrolled. Patient characteristics are listed in Table 1. Thirteen of 15 patients with T3/4 disease had fixation of the vocal cord at presentation, and disease in 2 patients was defined as T3 because of estimated tumor diameter on CT/MRI scan that exceeded 4 cm. Among 20 patients with node-positive disease, 3 had lymph node metastasis at level IV, and the others were confined to level II and/or level III. Two patients had histories of esophagectomy due to esophageal cancer at 7 and 10 years before enrollment, and 2 other patients had simultaneous superficial esophageal cancers that were successfully treated with endoscopic mucosal resections thereafter. Three patients were classified as Zubrod PS 2, otherwise all patients were PS 1. At the time of this analysis, 1 patient was lost to follow-up at 24 months without evidence of disease recurrence. Otherwise, all patients were followed for more than 2 years or until death, and the median follow-up period for surviving patients was 59 months (24–90 months).

Table 1. Patient characteristics.

Characteristics	No. of patients	%
Sex		
Male	32	91
Female	3	9
Age		
Median (range), y	61 (46–73)	
Subsite		
Pyriform sinus	30	86
Post cricoid	4	11
Posterior wall	1	3
Differentiation		
Moderately	17	49
Poorly	6	17
Not specified	12	34
T/N classification		
T2	20	57
N0	7	20
N1	3	9
N2a	1	3
N2b	8	23
N3	1	3
T3	12	34
N0	6	17
N1	1	3
N2a	1	3
N2b	4	11
T4	3	9
N0	2	6
N1	1	3
Stage		
II	7	20
III	10	29
IV	18	51
Volume of the primary tumor (mL)		
Median (range)	15 (3–49)	
<10	5	14
≥10, <20	17	49
≥20, <30	9	26
≥30	4	11

Completeness of the Protocol. Eight patients received up-front nodal dissection at 8 to 25 days (median, 17 days) before start of RT without serious postoperative complications. All of the 35 patients

completed RT and chemotherapy as planned with a median overall treatment time of 44 days (range, 40–48 days). All prolongations of overall treatment time for more than 6 weeks were due to public holidays and/or maintenance of the RT machine. Adverse events that were observed within 90 days after start of the treatments are listed in Table 2. It should be noted that all of the grade 3 adverse events were observed after the end of the treatment and no patients required interruption of RT and/or chemotherapy. Five patients required transient parenteral hyperalimentation to supplement decreased oral intake. However, 24 (69%), 33 (94%), and 35 (100%) patients recovered their normalcy of diet within 2, 4, and 7 weeks, respectively, after completion of the treatments. Although 3 patients required tracheostomy before start of the treatments because of tumor-related airway stenoses, all of them were able to achieve complete resolution of the tumor and were decannulated within 2 months after completion of the treatments. One patient experienced transient grade 3 thrombocytopenia immediately after completion of RT but recovered spontaneously within a week without suffering a symptomatic hemorrhagic accident.

Patterns of Failure. Four patients experienced local persistence or recurrence with ($n = 3$) or without ($n = 1$) nodal metastases. Otherwise, 3 patients, all of whom had node-negative disease at presentation, experienced nodal recurrences as first sites of relapses within irradiated volume of the boost RT in 2 patients, and at the periphery in 1 patient. All but 1 patient with unresectable, isolated nodal failures underwent successful salvage without serious postoperative complications. However, 1 patient died of subsequent nodal failure. Two other patients experienced distant metastases in the lungs as first site of relapse without evidence of locoregional recurrence. Both of these 2 patients originally had node-negative disease (T2 in 1 patient and T4 in 1 patient). One patient died of ischemic heart disease without evidence of disease recurrence at 41 months. Overall survival rate at 3 years was 91% (95% confidence interval, 81% to 100%). All of the disease recurrences at the primary sites were observed within 2 years, and local control rate at 2 years was 88% (79% to 99%), as shown in Figure 1. Nodal and distant metastasis rates at 2 years were 14% (3% to 26%) and 6% (0% to 15%), respectively. Progression-free survival at 2 years was 77% (63% to 91%). All of the 20 patients who had T2 disease did not experience local recurrence. However, 1 patient died of nodal recurrence at 13 months. On the other hand, 4 of the 15 patients who had T3/4 diseases experienced local recurrences. Local control rate at 2 years for patients with T3/4 disease was 73% (51% to 96%).

Table 2. Acute events.

Grade	0	1	2	3	4	5
White blood cell	18	12	5	0	0	0
Anemia	25	6	4	0	0	0
Thrombocytopenia	33	0	1	1	0	0
Mucositis due to radiation	0	6	17	12	0	0
Dysphagia-pharyngeal due to radiation	1	8	18	8	0	0
Creatinine	24	10	1	0	0	0
Nausea/vomiting	31	2	2	0	0	0
Worst overall	0	4	18	13	0	0

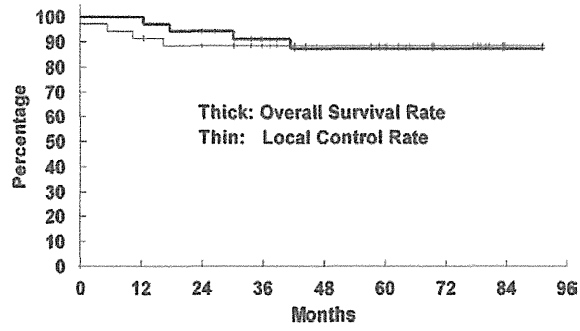

FIGURE 1. Kaplan–Meier estimates of overall survival and local control rates in patients with T2 to 4 primary tumor that was amenable to margin-free resection without bilateral or unresectable nodal metastasis who underwent chemotherapy-enhanced accelerated radiotherapy. Thick and thin lines represent overall survival and local control rates, respectively.

Primary tumors that showed superficial spread with an exophytic growth pattern had tumor volumes of less than 7 mL ($n = 5$), whereas patients that presented with endophytic tumors ($n = 30$) had tumor volumes of at least 10 mL on CT volumetry. Local control rate at 2 years for the former patients was 100%, contrasted to 87% (95% confidence interval, 74% to 99%) for the latter.

Late Adverse Events. One patient required 3 months of gastrostomy tube feeding and antibiotics for exposure of the thyroid cartilage to the pharyngeal cavity at 10 months, and another patient underwent repetitive balloon dilatation for pharyngeal stenosis without the need of taking a soft diet at 9 months. Both patients recovered their normalcy of diet thereafter and were alive and recurrence-free at 83 and 58 months, respectively. Otherwise, late radiation morbidities of grade 2 or greater were not observed. As a whole, all of the patients who were alive with their larynx retained their normal understandable speech without the need for a tracheostomy. Furthermore, all patients who were alive, including those who underwent salvage total laryngopharyngectomy, maintained their normal diets.

DISCUSSION

For laryngeal cancer, a clinical practice guideline for larynx-preserving approach was presented[17] based on

data accumulated from landmark studies.[25,26] The same principles are thought to be applicable to hypopharyngeal cancer. In this study, patients who had primary tumors that mostly localized within the hypopharynx and larynx without penetration of the thyroid cartilage and pharyngeal constrictor muscle were enrolled. These hypopharyngeal cancers had tumor volumes of approximately ≤30 mL, and better local control rate after RT than in patients with larger primary tumors as was suggested from retrospective studies.[19,27,28] Measurement of tumor volume is significantly influenced by interobserver variation and imaging modality used in volumetry.[29] However, the required precision for tumor volumetry to adequately predict radiocurability was considered as ±50% in a review of the literature.[30] Therefore, it is conceivable that most patients enrolled in this study had "intermediate-volume" tumors requiring total laryngopharyngectomy as a curative surgical approach and amenable to margin-free resections, but which were not categorized as having "low-volume" tumors.

When this study was being developed, however, a high percentage of patients with intermediate-volume hypopharyngeal cancers without advanced nodal diseases did not receive definitive CRT in many academic centers in Japan.[1,31] This was because the safety and efficacy of possible salvage surgery after CRT was empirically expected to be poor.[32,33] In addition, a recent multiinstitutional larynx-preserving trial using intensive CRT showed that, at 1 year, 23% of the patients were able to swallow only soft foods or liquids, and 3% could not swallow at all.[26] Other detrimental effects of concomitant high-dose chemotherapy with altered fractionation RT on long-term swallowing functions were also documented.[34,35] For patients with hypopharyngeal cancer with intermediate-volume primary tumors, clinical clarification of the following points were sought in this study: (1) altered fractionation RT alone is insufficient to satisfy the result; (2) however, 2 or more courses of concomitant chemotherapy not only could result in deterioration of function, but is unnecessary to achieve the outcome comparable to altered fractionation RT alone for early-stage, low-volume tumors[10,11]; (3) efforts to minimize the irradiated volume receiving CRT may be needed to prevent excessive vascular and/or connective tissue damage at the expected anastomosis site in possible salvage surgery; (4) for this purpose, up-front nodal dissection should be positively considered in patients with nodal disease spreading outside of the target volume for boost RT encompassing only the primary tumor with margins. Concomitant chemotherapy during the former part of RT was not done to eliminate unexpected local and/or systemic toxicity of chemotherapy that possibly interrupt timely administration of accelerated RT.[21] As a result, all patients completed the protocol treatment without an unplanned break, and all of the 4 patients who experienced local recurrences safely underwent salvage total laryngopharyngectomy.

More than 5 years were required to accumulate the 35 patients as expected at the time of protocol development. The principal conclusion of this study was the feasibility of this protocol. However, it should be emphasized that none of the 20 patients with T2 disease experienced local recurrence. Although 73% of local control rate at 2 years for T3/4 disease was observed in only 15 patients, the lower limit of the 95% confidence interval was 51%, which exceeded the results of a previous randomized study for larynx-preserving treatment in patients with resectable hypopharyngeal cancer.[3] Overall survival rate at 3 years was 91% with acceptable distant failure rate. These results showed that this regimen can become an alternative to more intensive CRT in patients who were eligible for this study.

This regimen is in contrast to the widely accepted benefit of concomitant chemotherapy delivered throughout RT. However, for certain patients with stage III/IV disease, low-volume disease could achieve satisfactory results after treatment without using intensive chemotherapy.[14,36] Incidence of grade ≥3 mucositis was 34% (12 of 35), which was comparable to results in previous studies regarding CRT with higher dose of chemotherapy.[26] However, it should be noted that all of the grade 3 mucositis occurred after completion of the protocol and most of the patients recovered their normalcy of the diet within 4 weeks, probably because of no additional injury to the mucous membrane after occurrence of serious mucositis in this regimen. In addition, grade ≥3 hematologic toxicity was observed in only 1 patient (3%). Given that bacterial colonization in patients with compromised immune reaction aggravates and prolongs severe acute mucositis,[37] lower bone marrow toxicity of this regimen is preferable to ameliorate chronic dysphagia as a consequential late effect.[16] As a result, no surviving patient experienced feeding tube dependency at ≥2 years in this study. Upfront nodal dissection followed by definitive RT with or without substandard chemotherapy for appropriately selected patients with small pharyngolaryngeal cancer with bulky N2/3 disease could achieve locoregional control rates equal to those who had N0/1 disease without compromise of survival.[38–41] Six percent of distant failure rate (none in patients who underwent up-front nodal dissection) in this study was in good agreement with these previous reports.[38,40,41] The survival benefit of adding intensive chemotherapy for the purpose of preventing distant failure had never been observed in patients with resectable disease and, at present, the value of intensive chemotherapy for these patients is recognized as improvement of locoregional control.[3,12,26] In this context, because of 88% preservation rate of functioning larynx with a low distant failure rate, this study including 20 patients with node-positive disease who were amenable to margin-free resections (8 required up-front nodal dissection)

should not be criticized based solely on substandard use of chemotherapy. Involvement of nodal metastasis outside of the sentinel area (ie, ipsilateral levels II and III) was reported as a significant factor of developing distant failure.[42] Because only 3 of 35 patients had gross nodal disease at the level IV, the results of this study might be relevant to a subsection of hypopharyngeal cancer patients having T2 or small T3/4 primary tumor with N0 to resectable N2 disease localized to the sentinel area (incipient N2), which should be considered in subsequent studies. The necessity of upfront nodal dissection only for prevention of excessive tissue damage may be negated in the intensity-modulated radiotherapy era.

Whether the results of this study were merely due to our patient selection in a single institutional setting, must be elucidated in larger, multi-institutional trials. However, the survival benefit of altered fractionation RT was already demonstrated in a meta-analysis.[43] Patients with hypopharyngeal cancer have relatively poor health status and high propensity of developing acute and/or late toxicities such as pneumonia and dysphagia. In this context, the benefit of intensive chemotherapy added to RT may be diminished and negated by its toxic effect when patients with hypopharyngeal cancer having relatively small tumor burdens are included in larynx preserving trials.[30] Therefore, testing separate strategies for patients with intermediate-volume primary tumor with N0 to incipient N2 disease was considered justifiable. Appropriateness of chemotherapy-enhanced accelerated RT was thought to be applicable even when intermediate-volume tumors were categorized as T3/4 disease in the current staging system with sophisticated imaging modalities. However, dosing of chemotherapy, role of induction chemotherapy, and molecular targeted therapy should be studied further with careful patient selection in these patients. In patients who have larger tumor burdens, reduced dose chemotherapy no longer achieved satisfactory tumor cure.[44,45]

In conclusion, accelerated fractionation RT with delayed concomitant chemotherapy as a radiation sensitizer was feasible and showed encouraging oncological and functional outcomes in patients with intermediate volume hypopharyngeal cancer who would otherwise have required total laryngopharyngectomy. Further study is warranted to test the appropriateness of this regimen for patients with hypopharyngeal cancer who have intermediate-volume, especially T2, primary tumor with N0 to incipient N2 disease in multi-institutional collaborations.

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Outcomes of Japanese breast cancer patients treated with pre-operative and post-operative anastrozole or tamoxifen

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The present study examined long-term efficacy outcomes in a subgroup of postmenopausal, estrogen receptor-positive Japanese breast cancer patients from the Pre-Operative "Arimidex" Compared with Tamoxifen trial, following pre-operative (3 months) and post-operative (5 years) adjuvant treatment with either anastrozole or tamoxifen. Patients with large, potentially operable, locally-advanced breast cancer were randomized to receive anastrozole (1 mg/day) plus tamoxifen placebo or tamoxifen (20 mg/day) plus anastrozole placebo pre-operatively. After surgery at 3 months, patients continued on the same study medication as adjuvant therapy for up to 5 years or until recurrence, intolerable toxicity or withdrawal of patient consent. Recurrence-free survival and overall survival were measured from the date of randomization to the date of recurrence or death, whichever occurred first. Patients were monitored for adverse events throughout the study period and up to 30 days following administration of the last study medication. During post-operative adjuvant therapy, 4/48 (8%) anastrozole and 25/49 (51%) tamoxifen patients experienced recurrence. There was a significant difference in recurrence-free survival between the two groups (hazard ratio 0.14; 95% confidence interval 0.05–0.41; $P = 0.0003$). There was a significant increase in overall survival with anastrozole (0.21; 0.05–0.96; $P = 0.0436$) and there were 2/48 (4%) and 10/49 (20%) deaths with anastrozole and tamoxifen, respectively. Most patients responding to pre-operative therapy remained recurrence-free. Sequential pre-operative/post-operative treatment with anastrozole resulted in lower recurrence and death rates, compared with tamoxifen. (*Cancer Sci* 2012; 103: 491–496)

Although several pre-operative trials comparing hormonal therapy with an aromatase inhibitor (AI) versus tamoxifen have reported the superior efficacy of AI in terms of primary tumor response, long-term follow-up outcomes from pre-operative and subsequent post-operative therapy have rarely been reported.[1–5] For instance, in the P024 neoadjuvant endocrine therapy trial, which compared 4 months' pre-operative letrozole versus tamoxifen, patients were treated with post-operative tamoxifen only, regardless of the randomized pre-operative treatment received.[6] Thus, it was not possible to evaluate the impact of a pre-operative and subsequent post-operative AI over tamoxifen on prognosis.

The Pre-Operative Arimidex Compared with Tamoxifen (PROACT) trial was a randomized, double-blind, double-dummy, multicenter study, conducted in the USA (12 centers), in Europe and the rest of the world (44 centers) and in Japan (25 centers) that compared anastrozole versus tamoxifen as pre-operative (12 weeks' treatment prior to primary surgery), in terms of objective response (OR), and subsequent post-operative (adjuvant) treatments in 451 postmenopausal women with large, operable, or potentially operable, locally-advanced, hormone receptor-positive (HR+) breast cancer. PROACT demonstrated that anastrozole was at least as effective as tamoxifen in the pre-operative phase, in terms of primary tumor response rate (40% *vs* 35% for the anastrozole and tamoxifen treatment groups, respectively), and more patients in the anastrozole group showed an improvement between feasible surgery at the baseline and actual surgery compared with those in the tamoxifen group. The effect of ethnicity on the response to treatment was also investigated and Japanese centers were included to provide a cohort of non-white patients. There were no specific treatment–ethnicity interactions, with respect to OR, between the Japanese patients and the rest of the population.[7] In the post-operative phase, PROACT was planned to continue for 5 years to investigate the long-term efficacy of anastrozole and tamoxifen in terms of recurrence-free survival (RFS: the time interval between randomization and disease recurrence or death, whichever occurred first) and overall survival (OS). However, when PROACT reached a median follow up of 3.8 years in the blinded phase, the study was unblinded and closed because the Arimidex, Tamoxifen, Alone and in Combination (ATAC) trial showed superior efficacy for anastrozole compared with tamoxifen in the post-operative adjuvant setting.[8] Furthermore, the combined analysis of data from two other prospective trials demonstrated the benefit of switching from adjuvant tamoxifen therapy to anastrozole after 2 years of treatment.[9]

In Japan, however, the PROACT study continued for a further 1.2 years, to meet regulatory commitments, stressing the importance of collecting data for anastrozole during post-operative adjuvant use in Japanese women with HR+ early breast cancer. At unblinding, the Japanese PROACT patients had the option to re-consent and receive either anastrozole or tamoxifen on an open-label basis, thus allowing them to complete a total of 5 years' follow-up.

This analysis reports the long-term outcomes for this subgroup of Japanese patients from PROACT who received anastrozole or tamoxifen as pre-operative and subsequent post-operative adjuvant treatment.

Patients and Methods

Study design and patients. The design of the main PROACT study (Clinicaltrials.gov identifier: NCT 00232661) has been previously described in detail.[7] Briefly, PROACT was designed

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to compare pre-operative therapy with anastrozole with tamoxifen in terms of OR in postmenopausal women with large, operable (T2 [≥3 cm], T3, N0–2, M0), or potentially operable, locally-advanced (T4b, N0–2, M0), estrogen receptor-positive (ER+) and/or progesterone-receptor positive (PgR+) breast cancer (histologically and cytologically proven using needle-biopsy specimens).[10] Secondary objectives included the comparison of post-operative therapy with anastrozole or tamoxifen in terms of RFS, OS, time to recurrence, and safety. Patients were randomized to receive anastrozole (1 mg/day) plus tamoxifen placebo or tamoxifen (20 mg/day) plus anastrozole placebo for 3 months before surgery (pre-operative phase). Concomitant chemotherapy was permitted, if considered appropriate by the investigator. Concomitant ketoconazole (or related systemic compounds) and any drugs that affect sex hormone status (e.g. HRT) were not permitted from randomization through to cessation of study therapy.

Eligible patients were to receive surgery at 3 months, and then continue receiving the same study medication as adjuvant therapy for up to 5 years or until recurrence, intolerable toxicity or withdrawal of patient consent. However, due to data demonstrating the superiority of anastrozole compared with tamoxifen in the post-operative setting,[8] the main study was closed at unblinding in all countries except Japan. Japanese patients continued to be assessed according to the study protocol and in accordance with the Declaration of Helsinki and applicable regulatory requirements. The study protocol was approved by the institutional review board and written informed consent was obtained from all patients.

Assessments. In the main PROACT trial, objective response rate at 3 months (pre-operative phase) was determined using ultrasound and caliper according to Response Evaluation Criteria in Solid Tumors (RECIST). The interaction between treatment and ethnicity (Japanese patients versus others) was also assessed for OR. Due to the continuation of PROACT in Japan, it was also possible to measure RFS and OS for this sub-population. By definition, RFS could include any of the following: death by any cause, distant metastases, loco-regional recurrence or disease progression (pre-operative phase). DFS (the length of time after treatment during which no disease was found) was also measured. OS was measured from the date of randomization to the date of death. After surgery, follow-up visits for RFS and OS occurred every 6 months for up to 5 years. Treatment compliance was determined by recording details of dispensed and unused medication for each individual patient. Patients were monitored for adverse events (AE) throughout the study period and up to 30 days following administration of the last study medication.

Statistical analysis. A logistic regression model with a treatment–ethnicity interaction term was used to calculate that 40 Japanese patients per treatment arm were required in order to detect, with 80% power, at a 5% significance level, a response rate of 15% improvement for patients receiving anastrozole versus tamoxifen in the overall study population, and a 15% decrease for patients receiving anastrozole versus tamoxifen in the Japanese patient subgroup.

In the main PROACT study, no formal statistical analysis could be performed on the data from the adjuvant period due to the early closure of the trial. However, in the Japanese substudy, RFS and OS were summarized by randomized study treatment in the intent-to-treat population by estimating the hazard ratio (HR) and two-sided 95% confidence intervals (CI) for anastrozole versus tamoxifen, derived from a Cox regression model. Overall RFS and OS were summarized using Kaplan–Meier methods. For time to recurrence, any patient who had not recurred was censored at the date of their last visit. For OS, any patient who had not died was censored at the date of last contact. Safety data were analyzed on the basis of treatment first received.

Table 1. Patient baseline characteristics in the Japanese intent-to-treat population and concomitant therapies during the adjuvant study

	Japanese patient cohort		Overall population	
	Anastrozole (*n* = 48)	Tamoxifen (*n* = 49)†	Anastrozole (*n* = 228)	Tamoxifen (*n* = 223)
Median age, years (range)	61.5 (51.4–84.7)	61.6 (51.4–81.3)	67.3 (48.7–91.5)	66.7 (44.1–95.9)
Median height, cm (range)	153.1 (140.0–167.5)	152.3 (138.0–163.1)	157.2 (140.0–178.0)	156.4 (137.0–173.0)
Median weight, kg (range)	55.5 (35.0–76.0)	55.0 (42.0–79.0)	67.3 (35.0–144.0)	67.3 (38.0–118.0)
Median body mass index, kg/m^2 (range)	23.7 (15.7–32.0)	23.6 (18.9–35.2)	27.3 (15.2–60.7)	27.5 (16.3–48.6)
Tumor dimension by ultrasound				
Mean, cm (range)	3.8 (1.7–9.0)	3.8 (1.8–6.3)	3.6 (1.1–9.5)	3.6 (0.4–8.9)
<4 cm, *n* (%)	29 (60.4)	32 (65.3)	147 (64.5)	148 (66.4)
≥4 cm, *n* (%)	19 (39.6)	17 (34.7)	81 (35.5)	75 (33.6)
ER and PgR status, *n* (%)				
ER+ and PgR+	32 (66.7)	27 (55.1)	159 (69.7)	152 (68.2)
ER+ and PgR−	15 (31.3)	21 (42.9)	56 (24.6)	59 (26.5)
ER− and PgR+	1 (2.1)	1 (2.0)	3 (1.3)	2 (0.9)
Feasible surgery, *n* (%)				
Breast-conserving	2 (4.2)	2 (4.1)	26 (11.4)	38 (17.0)
Mastectomy	46 (95.8)	47 (95.9)	185 (81.1)	168 (75.3)
Inoperable	0 (0)	0 (0)	17 (7.5)	16 (7.2)
Concomitant therapy received during the adjuvant study	Anastrozole (*n* = 48)	Tamoxifen (*n* = 43)†		
Any chemotherapy‡	10 (23.3)	20 (46.5)	–	–
Radiotherapy	18 (41.9)	17 (39.5)	–	–
Any chemotherapy in combination with radiotherapy	4 (9.3)	8 (18.6)	–	–

†Includes 12 patients who switched from randomized tamoxifen to receive open-label anastrozole. ‡Some patients received more than one type of chemotherapy. ER, estrogen receptor; PgR, progesterone receptor.

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Results

Patients. The first patient entered the PROACT study in October 2000. The last patient entered in 2002, finishing in December 2007. In total, 97 Japanese patients were randomized to receive neoadjuvant treatment with anastrozole (n = 48) or tamoxifen (n = 49). Patient demographics and characteristics at the baseline were well balanced in both groups, consistent with the overall population (Table 1). The disposition of patients throughout the study is summarized in Figure 1. During the pre-operative phase, 82 (85%) patients received endocrine therapy alone and 15 (15%) patients received chemotherapy in addition to endocrine treatment.[11]

Following pre-operative therapy and surgery, 86 (89%) patients (43 in each group) entered the post-operative phase of the study. After unblinding, 12 patients switched from tamoxifen to anastrozole and all other patients continued on their prior therapy. A total of 10 (23%) anastrozole and 20 (47%) tamoxifen patients received concomitant chemotherapy during the post-operative phase, although a similar number of patients received radiotherapy: 18 (42%) patients in the anastrozole group and 17 (40%) patients in the tamoxifen group. Treatment compliance throughout the whole study was high in both groups (94% in the anastrozole group and 95% in the tamoxifen group).

Recurrence-free survival. At a median follow-up of 62 months for both groups, 29 events had occurred, with recurrence rates of 8% (4/48) in the anastrozole group and 51% (25/49) in the tamoxifen group. All four events in the anastrozole group and 20/25 (80%) events in the tamoxifen group were confirmed before unblinding. There was a significant difference in RFS between patients in the anastrozole versus tamoxifen groups (HR 0.14, 95% CI 0.05–0.41; P = 0.0003) (Fig. 2a).

Overall survival. At a median follow up of 63 months for both groups, there had been two (4%) deaths in the anastrozole group (one before unblinding) and ten (20%) deaths in the tamoxifen group (seven before unblinding), resulting in a significant increase in OS in the anastrozole group compared with the tamoxifen group (HR 0.21, 95% CI 0.05–0.96; P = 0.0436) (Fig. 2b).

Correlation between pre-operative objective response and recurrence-free survival. Of the 31 patients who responded to pre-operative anastrozole or tamoxifen therapy, 26 (84%) remained recurrence-free (15/17 [88%] and 11/14 [79%] in the anastrozole and tamoxifen groups, respectively). The number of patients with stable disease was the same in both groups (n = 26). All 26 patients with stable disease remained recurrence-free in the anastrozole group, whereas 13/26 (50%) of patients had a recurrence event in the tamoxifen group (Table 2).

Tolerability. As one patient (randomized to tamoxifen) did not receive treatment, 96 patients comprised the safety population. Fewer patients reported AE and serious AE (SAE) in the anastrozole group than in the tamoxifen group. Hot flashes were the most commonly reported treatment-related AE, with a similar incidence in each group (Table 3). Of the SAE, cerebral infarction and endometrial hyperplasia were observed in two

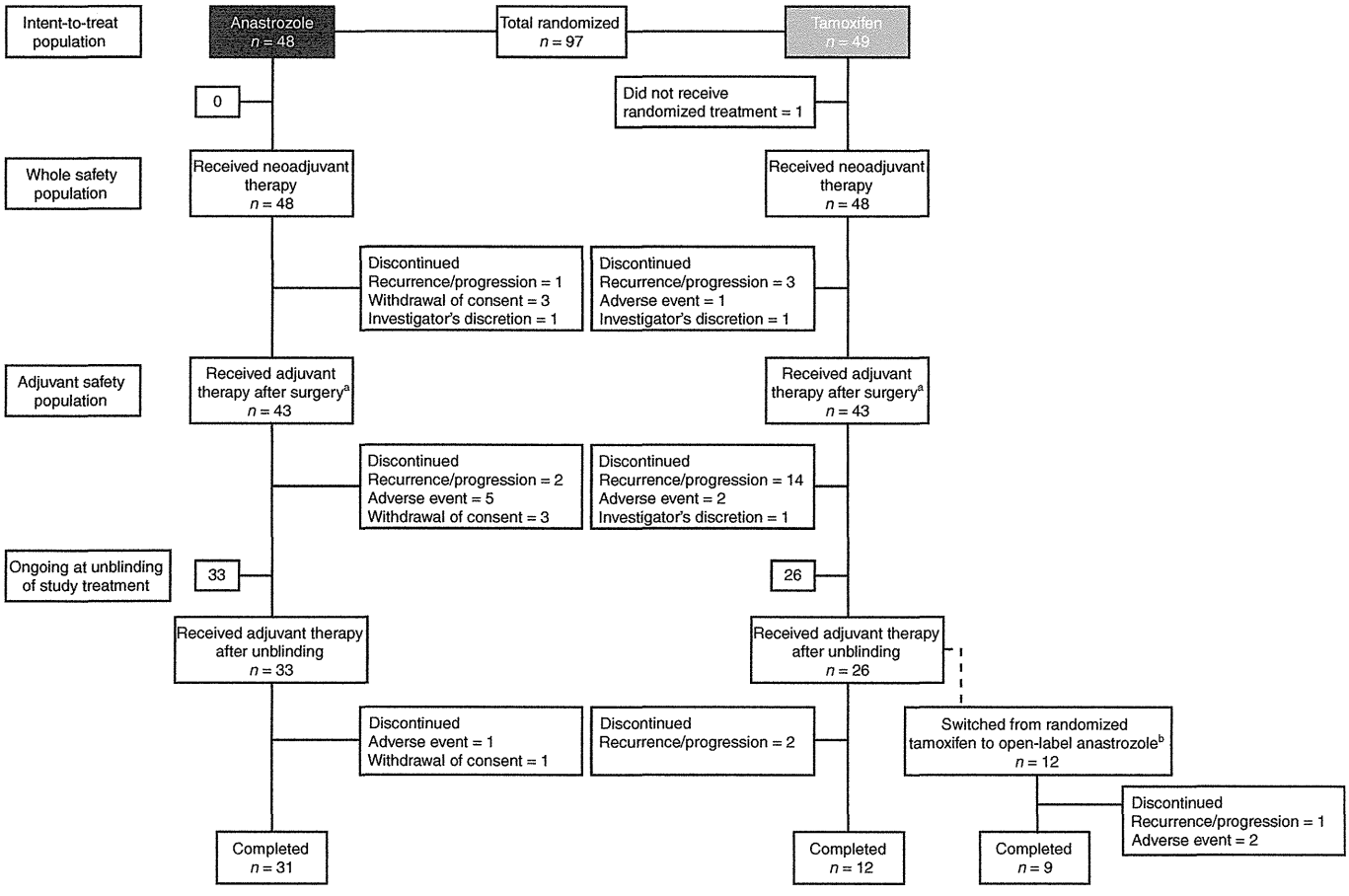

Fig. 1. Patient disposition (completion or discontinuation). [a]The date of surgery was used to define the end of the neoadjuvant period, as detailed in the statistical analysis plan. [b]Twelve patients who received randomized tamoxifen before unblinding opted to switch to receive open-label anastrozole. No patients who received randomized anastrozole before unblinding opted to switch to receive open-label tamoxifen.

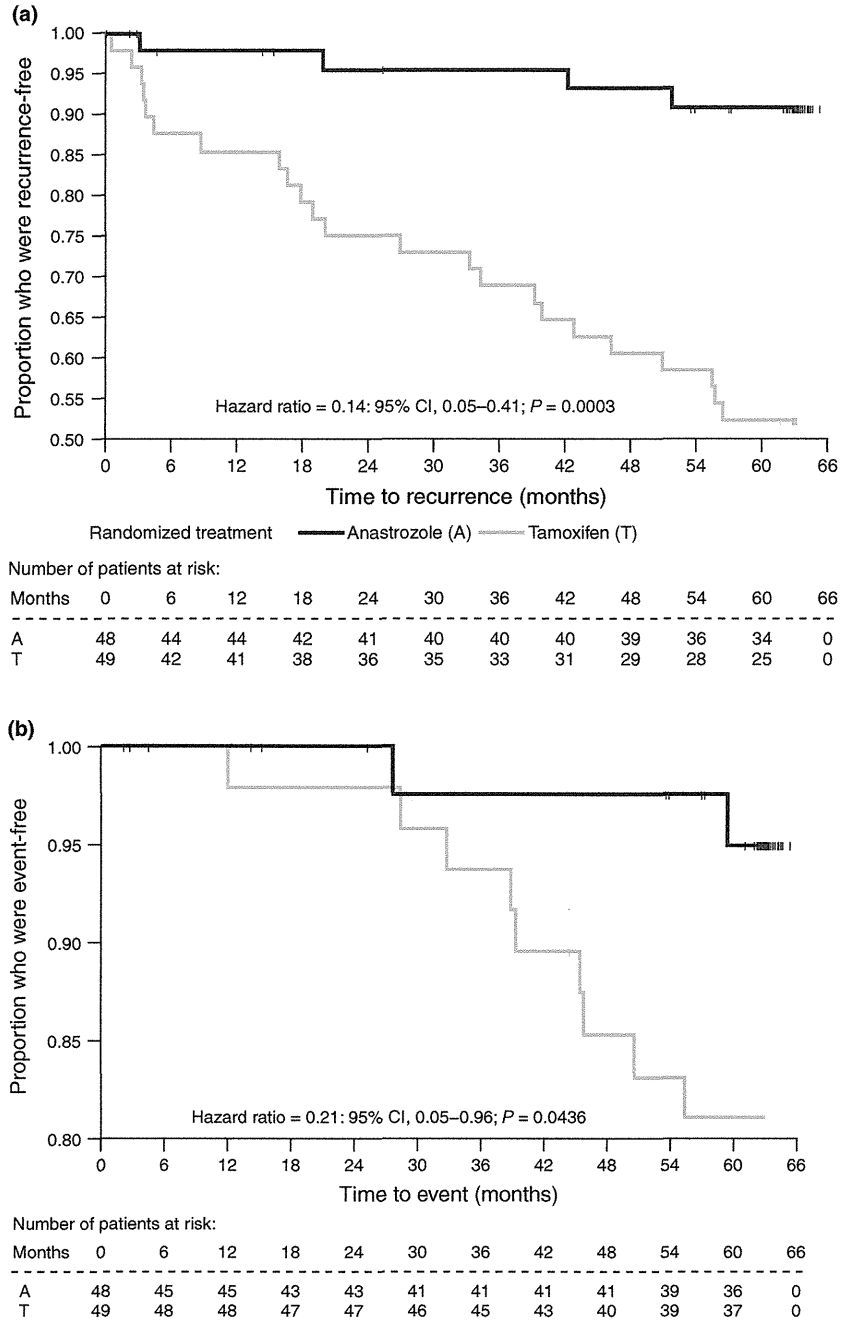

Fig. 2. Kaplan–Meier plot for: (a) recurrence-free survival (all randomized Japanese patients) and (b) overall survival (all randomized Japanese patients). Recurrence-free survival is defined as time to first event, where event is either death or recurrence. Overall survival is defined as time to death. Patients who did not recur or die have been censored; tick marks indicated censored patients. CI, confidence interval.

patients from the tamoxifen group, while no SAE were reported in the anastrozole group. There were no myocardial infarctions, fractures or thrombolytic events in either treatment group. AE leading to death were seen in one patient with pancreatic carcinoma and in another patient with cerebral infarction in the tamoxifen group.

Discussion

While the superiority of the AI (including anastrozole and letrozole) over tamoxifen is well established in the post-operative adjuvant setting, the efficacy of the AI over tamoxifen given as pre-operative and subsequent post-operative treatments has yet to be reported. We believe that this is the first randomized study to make such a comparison. At 5 years' follow-up in Japanese patients, we found that in the anastrozole group, 92% of patients were free from recurrence and 96% of patients were still alive. In the tamoxifen group, 49% of patients were free from recurrence and 80% of patients were still alive after 5 years. Thus, patients treated with anastrozole had significantly lower risk of disease recurrence and death than those treated with tamoxifen.

Unexpectedly, the difference in RFS between anastrozole and tamoxifen was substantial, and a significant difference in OS was also observed. The reduction in RFS (HR 0.14, 95% CI

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Table 2. Correlation between pre-operative objective response (Response Evaluation Criteria in Solid Tumors by ultrasound) and recurrence-free survival

	Number of patients (%)			
	Anastrozole (n = 43) Recurrence-free survival		Tamoxifen (n = 43) Recurrence-free survival	
	Yes	No	Yes	No
Objective response				
Complete response	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.3)
Partial response	15 (34.8)	2 (4.7)	10 (23.3)	2 (4.7)
Stable disease	26 (60.5)	0 (0.0)	13 (30.2)	13 (30.2)
Progressive disease	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.0)

Responders are defined as those patients being assessed as having a complete or partial response. Non-responders are defined as those patients being assessed as progressing or having stable disease or not evaluable.

Table 3. Most commonly reported treatment-related adverse events (AE) (≥2%),† whole safety population

	Number of patients (%)‡	
	Anastrozole (n = 48)	Tamoxifen (n = 48)§
Hot flash	8 (17)	10 (21)
Aspartate aminotransferase increased	2 (4)	7 (15)
Alanine aminotransferase increased	2 (4)	6 (13)
Hepatic steatosis	3 (6)	4 (8)
Hyperhidrosis	3 (6)	4 (8)
Arthralgia	3 (6)	3 (6)
Genital discharge	0 (0)	5 (10)
Headache	5 (10)	0 (0)
Nausea	2 (4)	3 (6)
Alopecia	0 (0)	4 (8)
Back pain	1 (2)	3 (6)
Dizziness	3 (6)	1 (2)
Hypertension	3 (6)	1 (2)
Osteoporosis	3 (6)	1 (2)
Endometrial hypertrophy	0 (0)	3 (6)
Musculoskeletal stiffness	3 (6)	0 (0)

†Considered by the investigator to be related to randomized drug treatment. AE categorized according to the National Cancer Institute Common Terminology Criteria Version 2.0 wherever possible. ‡Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. §Includes 12 patients who switched from randomized tamoxifen to receive open-label anastrozole.

0.05–0.41; $P = 0.0003$) with anastrozole versus tamoxifen observed in this study was much greater than that in the ATAC trial at 5 years' follow-up (HR 0.87, 95% CI 0.78–0.97; $P = 0.01$).[8] Furthermore, no significant difference in OS was reported in the ATAC trial between anastrozole and tamoxifen.[8] The latest analysis of ATAC data (at a 10-year median follow up) has confirmed a significant difference for anastrozole versus tamoxifen in RFS (HR 0.91, 95% CI 0.83–0.99; $P = 0.04$) in the overall population, but no significant differences in OS (HR 0.97, 95% CI 0.88–1.08; $P = 0.6$).[12]

The reason why the efficacy of anastrozole was so great in this long-term follow up for a cohort of Japanese patients from the PROACT trial is unclear. One potential suggestion is that a number of patients were not included in the adjuvant treatment phase who did not respond to neoadjuvant treatment (5/48 patients in the anastrozole group and 6/49 patients in the tamoxifen group). It is possible that this extra level of selection or censorship might, therefore, have led to a slightly higher OS and RFS rate compared with the ATAC trial. Another possible explanation lies in the difference in the proportion of patients with CYP2D6 genotypes of decreased or no activity between Asians (approximately 30%) and white people (approximately 10%),[13] because recently these genotypes have been shown to be associated with a poor response to tamoxifen,[14–16] although such an association remains to be established.[17]

In this study, twice as many tamoxifen patients received concomitant chemotherapy and more tamoxifen patients were ER+/PgR− or ER−/PgR+, compared with anastrozole patients. In general, concomitant chemotherapy would be expected to improve clinical response. In the main PROACT study, in both treatment arms, OR rates were numerically higher for patients who received both endocrine and chemotherapy compared with patients who received endocrine therapy alone, indicating that concomitant chemotherapy improves response.[7] Therefore, the greater use of concomitant chemotherapy in the tamoxifen arm of the Japanese cohort would be expected to improve response compared with the anastrozole arm, which, if anything, would underestimate the effect of anastrozole. These HR imbalances between the two groups could have had a bearing on the RFS and OS results. However, an adjusted Cox regression analysis was not performed due to the small patient population. Because the PROACT study design did not include a comparison of Japanese versus matched non-Japanese data, we must emphasize that the RFS and OS benefits with anastrozole observed in this *post-hoc* analysis might only apply to the subgroup of Japanese patients examined in this study.

Of the patients who responded to pre-operative treatment with anastrozole or tamoxifen, the majority remained recurrence-free; that is DFS appeared to be similar between the anastrozole (88%) and tamoxifen groups (79%). However, among patients who had stable disease in the pre-operative phase, DFS in the tamoxifen group (50%) was much worse than for the anastrozole group (100%). In the results of the National Surgical Adjuvant Breast and Bowel Project protocols B-18 and B-27, pathological response, rather than clinical objective response to pre-operative chemotherapy, was significantly correlated with treatment outcome in terms of RFS and OS.[18,19] We have previously reported the results of a comparison of objective clinical responses versus histopathological tumor responses in the same cohort of Japanese patients from PROACT.[11] Although the objective clinical response rate (according to RECIST assessed by ultrasound) in the pre-operative phase was similar for anastrozole versus tamoxifen (40% and 33%, respectively; Table 2), the difference in the histopathological response rate (i.e. a degenerative change in one-third or more of constituent carcinoma cells, according to Pathological Response Criteria for Breast Cancer as defined by the Japanese Breast Cancer Society)[10] was numerically greater (35% *vs* 12%, respectively), although there was no pathological complete response in either treatment arm.[11] This difference in histopathological response between the two groups might reflect the effectiveness of the post-operative treatment. The superiority of the AI over tamoxifen in the pre-operative and post-operative settings has also been corroborated in previous studies comparing letrozole versus tamoxifen, in which letrozole has led to statistically significant improvements in overall response and breast-conserving surgery in the pre-operative setting[1,20] and fewer early relapses in the post-operative setting, although OS was not significantly different to tamoxifen.[21] In this study, the safety profiles of anastrozole and tamoxifen for a Japanese patient cohort were similar and consistent with those observed in previous studies.[5,8]

In conclusion, this long-term follow up of the PROACT study has shown that pre-operative and subsequent post-operative adjuvant therapy with anastrozole might lead to a lower recurrence and death rate compared to tamoxifen in a Japanese patient subgroup. Because this study started in 2000, it was not possible to further classify the participating patients into luminal type A or B categories, or to determine their human epidermal growth factor receptor 2 or Ki67 status. Nonetheless, the results from this trial suggest that sequential pre-operative and post-operative anastrozole treatment is a suitable treatment strategy for HR+ postmenopausal breast cancer patients, in particular those with relatively large tumors and lower-risk oncotype profiles. Further research involving a greater number of patients is needed to confirm our present observations, particularly in relation to any confounding factors such as concomitant chemotherapy.

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Disclosure Statement

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Paradigm shift in axilla surgery for breast cancer patients treated with sentinel node biopsy

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Abstract
Background Sentinel node biopsy (SNB) is a standard technique for the diagnosis of regional lymph node metastases in clinically node-negative breast cancer patients. In the case of pathologically negative sentinel lymph nodes (SLN), axillary lymph node dissection (ALND) can be avoided.
Methods Recent clinical studies on SNB in breast cancer were reviewed regarding the pathological and molecular diagnosis of SLN, the tools used to predict non-SLN metastases, the prognostic significance of isolated tumor cells (ITC) and micrometastases (MIC), and axilla surgery.
Results ITC or MIC in SLN was associated with worse survival in patients treated with SNB alone or SNB followed by ALND. However, this effect was limited and adjuvant therapy improved survival. If T1 and one SLN-positive breast cancer patients are treated with whole-breast irradiation and adjuvant therapy, additional ALND may not be necessary.
Conclusions SNB without ALND can be adopted for patients with a small number of SLN metastases. Although the lack of apparent regional lymph node recurrence, similar to tumor dormancy, cannot be fully explained, ALND should be performed in cases that are highly suspected to be non-SLN metastases.

Keywords Breast cancer · Micrometastases · Isolated tumor cells · Sentinel lymph nodes

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Introduction

Forty years ago, the National Surgical Adjuvant Bowel and Breast Project (NSABP) B-04 was planned to evaluate the utility of extensive breast surgery [1]. On the basis of the results of 25 years of follow-up, total mastectomy followed by immediate axillary lymph node dissection (ALND) did not affect overall survival (OS) for clinically node-negative and node-positive breast cancer patients in comparison with delayed ALND in cases of regional lymph node recurrence [2]. This result should be considered with caution, because adjuvant therapy was not performed in the 1970s. However, the initial recurrence rate of regional lymph nodes was unexpectedly low (18%) for clinically node-negative breast cancer patients treated with total mastectomy alone, in whom the incidence of nodal metastases had been estimated to be 30% based on the pathological results of patients who had been randomized to receive radical mastectomy. Although this discrepancy, similar to tumor dormancy, is not understood, it raises the clinical issue of whether ALND is appropriate for clinically node-negative breast cancer patients. A new era of axilla surgery has arisen since the sentinel node concept in breast cancer was proposed 20 years ago [3]. Sentinel lymph nodes (SLN) are defined as the first nodes that drain lymphatic flow from solid tumors [4]. This concept was proven and accepted in early stages of breast cancer and melanoma on the basis of the results of feasibility studies on SNB followed by regional lymph node dissection [5, 6]. To evaluate the necessity of axilla surgery for clinically node-negative breast cancer patients, several randomized trials compared SNB with SNB followed by ALND in breast cancer at the end of the 1990s [7–10]. In this article, optimal surgical management in the axilla will be discussed from the perspective of the SLN concept in breast cancer.

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Current status of sentinel node biopsy in Japan

To confirm the reliability and safety of SNB in Japanese breast cancer patients, a prospective study on SNB was organized in 2008 by our society, the Japanese Breast Cancer Society. Eighty-one institutes and community hospitals participated in the study. The overall success rate was 98% in over 11,000 cases of dye-guided and/or radioisotope (RI)-guided SNB [11]. In addition, indigocarmine and indocyanine green (Daiichi Sankyo Co., Tokyo, Japan) used for dye-guided SNB were less allergic than isosulfan blue when injected transcutaneously. On the basis of these results, the Japan Ministry of Health, Labour, and Welfare approved dye-guided and/or RI-guided SNB in September 2009. Indigocarmine, indocyanine green, 99m-technetium-labelled tin colloid and 99m-technetium-labelled phytate (Nihon Medi-Physics, Tokyo, Japan) are available as tracers for lymphatic mapping in breast cancer, and national health insurance covers the cost of SNB.

Clinical relevance of micrometastases in sentinel lymph nodes

Although ALND is not recommended for SLN-negative [pN0(sn)] breast cancer at a routine pathological examination, occult metastases could be found more frequently if SLN are examined in greater detail. On the basis of some retrospective studies, the prognostic significance of occult metastases detected in pathologically node-negative breast cancer remains debatable [12, 13]. Unfortunately, there has been no large prospective study on occult metastases, because a detailed pathological examination of all lymph nodes obtained by ALND is considered to be too time-consuming for an institutional laboratory. In contrast, an average of only 2 nodes are needed for the SLN approach to breast cancer. Thus, a more detailed examination in SLN can provide more precise information on nodal metastases. In 2002, the International Union Against Cancer (now the Union for International Cancer Control, UICC) proposed a new classification of lymph node metastases, especially SLN metastases (Table 1) [14]. Isolated tumor cells (ITC) were thought to have no apparent biological activity to disseminate into tumor lymphatics and vessels, but this hypothesis remains uncertain. Regarding the intervals and sections of lymph node specimens and staining methods for detecting ITC and micrometastases (MIC), a standardized pathological examination is not yet available. The American Society of Clinical Oncology recommended pathological examination of SLN at an interval of 2 mm in tissue specimens [15]. On the other hand, the European working group of breast pathology recommended 2 mm as a minimum standard for the identification of SLN metastases, because some institutes in Europe have used heterogeneous definitions of ITC and MIC [16]. This group concluded that ITC and MIC in SLN might be shown to have clinical relevance in the future.

Table 1 Pathological nodal classification according to TNM staging organized by UICC

Classification	Size of metastases
Isolated tumor cells (i)	>0, ≤0.2 mm or cluster of fewer than 200 cancer cells
Micrometastases (mi)	>0.2, ≤2 mm and in 1–3 lymph nodes
Macrometastases	>2 mm
Non-morphological (mol)	>0 mm

Designated code abbreviations are given in parentheses

Usually hematoxylin–eosin (HE) staining is performed in practice and immunohistochemistry (IHC) staining is helpful for clearly detecting ITC and MIC in SLN. Veronesi et al. [7] first reported a randomized trial to compare SNB with SNB followed by immediate ALND for stage I breast cancer patients. In this study, a pathological examination was performed for both SLN and non-SLN. They examined SLN metastases in 15 pairs of frozen sections cut at 50-μm intervals. If residual tissue was left, additional pairs of sections were made at 100-μm intervals until the SLN had been sampled completely. If the SLN stained with HE were diagnosed as negative, an additional diagnosis was performed based on IHC staining in SLN. In addition, non-SLN were diagnosed by HE staining in 3–6 sections cut several 100 μm apart. A detailed examination revealed that 175 of 516 cases (34%) with stage I disease had positive nodes. Sixty of these (34%) had ITC or MIC in SLN alone and only 10 (17%) had additional metastases in non-SLN. On the basis of these results, occult metastases in SLN could be frequently found even in a small disease, but additional ALND could be omitted in cases with ITC or MIC in SLN alone.

Instead of a pathological workup, there have been rapid advancements in the molecular diagnosis of SLN. The one-step nucleic acid amplification (OSNA) assay is commercially available in Japan and Europe. This assay is highly sensitive and specific for the diagnosis of SLN metastases and has been shown to be highly reproducible in inter-institutional studies [17–19]. However, it has some limitations compared to the pathological diagnosis of SLN by HE staining. First, the OSNA assay measures the expression of cytokeratin (CK) 19 mRNA, and some breast cancer cases exhibit a very low expression of this mRNA. In CK19-negative cases, SN metastases may be overlooked. Second, the cutoff point of this assay is set for the

Table 2 Concordance between pathological nodal diagnosis and OSNA assay

OSNA assay	Pathological diagnosis (no. of nodes)				Concordance		
	NEG	ITC	MIC	MAC	Sensitivity (%)	Specificity (%)	Accuracy (%)
Ref. [17]							
−	263	13	2	0			
+	4	0	3	6	95.6	98.6	98.2
++	0	0	0	34			
Ref. [18]							
−	348	0	6	4			
+	18	3	7	–	87.7	94.3	93.1
++	0	0	–	64			
Ref. [19]							
−	854	14	22	9			
+	29	0	12	9	77.5	95.8	93.4
++	8	1	9	77			

NEG negative, *ITC* isolated tumor cells, *MIC* micrometastases, *MAC* macrometastases, *OSNA* one-step nucleic acid amplification

	Histology	NG	LVI	Mulifocality	ER/PR	HER2	SLN mets	T size	SLN size	Method	Age
MSKCC nomogram [22]	✔	✔	✔	✔	✔		✔	✔	✔	✔	
MD Anderson score [23]			✔	✔	✔	✔	✔	✔		✔	✔
Mayo nomogram [24]					✔		✔		✔	✔	
Tenon score [25]							✔		✔	✔	
Masaryk nomogram [26]	✔		✔	✔			✔	✔	✔		
Stanford nomogram [27]			✔					✔	✔		

Check mark represents factors for predicting non-SLN metastases.

NG nuclear grade, *LVI* lympho-vascular invasion, *SLN mets* number or proportion of positive SLN in all SLN detected, *T size* tumor size, *SLN size* size of the largest SLN metastases including extracapsular invasion, *Method* method for the detection of SLN metastases, *MSKCC* Memorial Sloan-Kettering Cancer Center

Fig. 1 Factors used in predictive tools for non-sentinel lymph node involvement in breast cancer

detection of MIC in lymph nodes. ITC in SLN may sometimes show negative results with the use of this assay (Table 2). However, a recent study demonstrated that this assay using a whole SLN detected cases with MIC more frequently than intraoperative diagnosis of SLN using frozen sections cut at 2-mm intervals did (8.7 vs. 4.5%) [20]. Thus, this assay is as reliable as a breast pathological examination for the detection of SLN metastases. If ITC in SLN is essential when considering adjuvant therapy to achieve a cure, a permanent diagnosis in SLN stained with HE and/or IHC should not be discarded in favor of an OSNA assay.

Tools for predicting non-sentinel lymph node metastases

In general, SLN metastases are identified in about 30% of clinically node-negative breast cancer patients, and half of those with positive SLN have only SLN metastases [5]. On the other hand, 40% of cases with macrometastases (MAC) in SLN have a higher probability of non-SLN metastases. Wada et al. [21] calculated the probability of non-SLN metastases using predictive factors for SLN-positive breast cancer patients who underwent SNB followed by ALND. Of the 185 cases analyzed in their study, 81 (44%) had SLN and non-SLN metastases, including 9 (26%) of the 34 cases with ITC or MIC in SLN and 72 (48%) of the 151 cases with MAC in SLN. A multivariate analysis demonstrated that tumor size, size of the largest SLN metastases, proportion of positive SLN in all SLN detected, and lymphatic invasion of the tumor were independent predictive factors of non-SLN metastases. When one predictive factor, among tumor size greater than 2.0 cm, MAC in SLN, all positive SLN (100%), or positive lymphatic invasion, was identified, the probability of non-SLN metastases was calculated to be 25%. Many investigators have proposed tools for predicting non-SLN metastases [22–27] (Fig. 1). Lympho-vascular invasion, multifocality, number or proportion of positive SLN, tumor size, size of the largest SLN

metastases, and methods for the detection of SLN metastases are common factors that are used for calculations with these tools, and with any tool the area under the receiver operating characteristic curve is around 0.8. Ultrasound, CT, and MRI are also important for detecting nodal metastases in axilla. Retrospective studies have shown that the incidence of MAC in non-SLN ranges from 0 to 13% and from 0 to 18% for breast cancer patients with ITC and MIC in SLN, respectively [21, 28]. Even if the probability of non-SLN metastases is very low using these tools and diagnostic imaging, occult metastases in non-SLN may continue to survive in ITC- or MIC-positive breast cancer patients treated with SNB alone.

Prognostic significance of sentinel lymph node metastases

Recently, several randomized trials have compared SNB with SNB followed by ALND for T1-2N0 breast cancer patients. NSABP B32 demonstrated that ALND did not improve the prognosis for pN0(sn) breast cancer patients [8]. OS at 8 years after randomization was 91.8% in 1,975 patients treated with SNB followed by ALND and 90.3% in 2,011 patients treated with SNB, and the unadjusted hazard ratio was 1.20 ($p = 0.12$). In this study, the prognostic significance of occult metastases was also evaluated prospectively in a blinded manner [29]. Paraffin blocks of SLN were routinely sliced at approximately 2.0-mm intervals and were diagnosed as negative by HE staining. In addition, sections of pathologically negative SLN were sliced at approximately 0.5 and 1.0 mm deeper in the surface and centrally reviewed pathologically using HE and IHC staining. Of the 3,887 breast cancer patients with pN0(sn) at a routine examination, 616 (15.9%) showed occult metastases in SLN: ITC and associated clusters in 430 (11.1%), MIC in 172 (4.4%), and MAC in 14 (0.4%) were detected in SLN. The estimated 5-year OS and 5-year disease-free survival (DFS) in breast cancer patients with occult metastases and those with no occult metastases were 94.6 and 95.8%, and 89.2 and 92.5%, respectively. Log-rank tests demonstrated that occult metastases in SLN significantly lowered OS and DFS in patients who were diagnosed as pN0(sn) at a routine examination ($p = 0.03$ and 0.02). However, the absolute difference in the 5-year OS (1.2%) was too small to justify a detailed examination of initially negative SLN. Interestingly, adjuvant endocrine therapy improved OS for hormone-sensitive breast cancer patients despite occult metastases in SLN. An SNB trial in the Netherlands reported a similar finding that adjuvant therapy improved DFS in breast cancer patients with ITC or MIC in SLN [30]. Those results suggest that, in clinical practice, the pathological examination of SLN should involve HE staining of tissue specimens cut at 2-mm intervals. Additional IHC staining is not recommended for the diagnosis of SLN metastases. Adjuvant therapy based on the tumor characteristics is essential for improving the patient's outcome.

How should we perform axilla surgery for breast cancer patients?

The American College of Surgeons Oncology Group (ACOSOG) Z0011 conducted a study in 1999 to optimize axilla surgery for early breast cancer patients who had a small number of positive SLN. Patients who had one or two positive SLN were eligible and randomized to receive either SNB alone or SNB followed by ALND. Adjuvant therapy was performed at the physician's discretion. OS was the primary endpoint, which led to a one-sided hazard ratio of less than 1.3, indicating that SNB alone is not inferior to ALND. Although 1,900 patients were required to confirm this hypothesis, the study was closed in 2004 because of the unexpectedly low number of deaths in the two treatment groups. Eventually, 891 patients were enrolled. At a median follow-up of 6 years, 5-year OS was 91.8% for 445 patients treated with SNB followed by ALND and 92.5% for 446 patients treated with SNB alone. Locoregional recurrence was seen in 16 and 12 patients, respectively [31]. The hazard ratio for OS was 0.87 after adjusting for age and adjuvant therapy (90% confidence interval, 0.62–1.23). These results suggest that breast cancer patients with one or two positive SLN can avoid ALND to prevent regional lymph node recurrence. However, this study has some limitations. First, approximately 70% of patients had T1 breast cancer, 60% had one positive SLN only, and 35% had MIC in SLN only. Such cases were expected to have a low risk of additional metastases in non-SLN. Second, whole-breast irradiation was a protocol treatment and level I axilla might be irradiated with a standard opposing tangential field. Third, the 5-year OS was similar among patients who underwent SNB alone in NSABP B32 and ACOSOG Z0011, even though they were in different cohorts of nodal metastases (95.0 and 92.5%). The risk of recurrence does not seem to have been high for patients in the latter study compared to those in the former study.

Conclusions

SNB can be used to avoid unnecessary ALND for patients with ITC as well as those with pN0(sn). ITC or MIC in SLN influences the patient's outcome regardless of the pathological or molecular diagnosis, and thus adjuvant

therapy should be used in such cases. If T1 and one SLN-positive breast cancer patients are treated with whole-breast irradiation and adjuvant therapy, additional ALND may not be necessary. Although non-SLN metastases exist in the axilla for some SLN-positive breast cancer patients, low locoregional recurrence was observed after a long follow-up in both NSABP B32 and ACOSOG Z0011, as well as in NSABP B04. This phenomenon, which resembles tumor dormancy, should be further investigated to better understand the relationship and interaction between the host defense and breast cancer.

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Conflict of interest None declared.

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