Material and Methods: The ASTRRA study is a multi-center, open-labelled, randomized, phase III study targeting 1234 patients from 36 centers in Korea and first subjects in (FSI) was in April, 2009. The ASTRRA study has been designed to compare DFS between the OFS + tamoxifen group and tamoxifen only group in premenopausal breast cancer patients. All the patients will be premenopausal prior to chemotherapy, less than or equal to 45 years of age with estrogen receptor positive (ER+ve) who have undergone a surgery for primay tumor, received an adjuvant chemotherapy±radiotherapy for their stage I, II or III breast cancer. At 0, 6, 12, 18 and 24 months since the baseline assessment, the ovarian function status will be evaluated by menstruation status or serum FSH level. If the patients are regarded as premenopausal, they will be randomized into the OFS + tamoxifen group or tamoxifen only group. All the patients who were eligible at the baseline for further follow-up will be followed up until 5 years for assessing primary and secondary objectives. All the patients will complete taking tamoxifen 20 mg/day for 5 years if they remain in the study. OFS will be done by administration of goserelin for 2 years.

Results: The main study endpoints are 5 year DFS rate, overall survival, and the tolerability of goserelin and tamoxifen. This study is now enrolling patients (208/1234) with good recruitment rate.

Conclusions: This study is expected to complete recruitment April 2011 and there could be an interim-analysis of the study after recruitment completion. The ASTRRA study is one of the largest study evaluating the role of OFS after chemotherapy and the study would be able to answer some important questions which is still controversial.

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Comparison of sonographic and pathologic measurements of breast tumour size after preoperative chemotherapy based on intrinsic subtypes

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Background: Breast ultrasonography (US) is used for measurement of the size of breast tumors due to its ease of use, simplicity and low invasiveness. However, tumor size measured by US often differs from that determined pathologically after preoperative chemotherapy, and this can make it difficult to determine the required extent of resection in breast-conserving surgery (BSC). Therefore, we examined whether the difference between sonographic and pathologic measurements could be reduced by consideration of intrinsic subtypes.

Material and Methods: 140 breast tumors underwent neoadjuvant treatment for Stage II-III breast cancer between 2003 and 2008 were classified into four subtypes based on ER, PgR and HER2 expression determined by immunohistochemistry. These were defined as the luminal A, luminal B, HER2 and triple negative (TN) subtypes. Tumors with a difference of ±1 cm between the long axis measured by US and pathologically were classified as correctly estimated by US. Tumors for which the US diameter was shorter than the pathologic diameter by more than 1 cm were considered to be underestimated by US, and those that were longer than the pathologic diameter by more than 1 cm were considered to be overestimated by US. The rates for correct, under and overestimation and the margin-positive rate in BCS (tumor resected with a 2-cm margin) were determined for each subtype.

Results: The rates of correct, under and overestimation of the tumor size in all patients were 69%, 20% and 11%, respectively. For the luminal A, underestimation occurred in 30% of cases, but overestimation in only 3%. In contrast, the sizes of the HER2 and TN were underestimated in 0% and 4% of cases, but overestimated in 28% and 19%, respectively (Table 1). These data differed significantly in each group ($P < 0.01$). BCS was performed in 97 cases and the margin was positive in 20 of these cases (21%). The margin-positive rate for the luminal A was significantly higher than those for the other three subtypes ($P = 0.04$).

Table 1

Estimate	Subtype			
	Luminal A	Luminal B	HER2	TN
Under estimate	22 (30%)	5 (22%)	0 (0%)	1 (4%)
Correct estimate	49 (67%)	14 (61%)	13 (72%)	20 (77%)
Over estimate	2 (3%)	4 (17%)	5 (28%)	5 (19%)

Conclusions: A comparison of sonographic and pathologic measurements of breast tumor size after preoperative chemotherapy was performed based on intrinsic subtypes. The tumor size for the luminal A tended to be underestimated before BCS, whereas the sizes of the HER2 and TN tended to be overestimated. These findings indicate that the subtype should be considered in determination of the surgical resection range using diagnostic ultrasound after preoperative chemotherapy.

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Comparison of 6 cycles versus 4 cycles of neoadjuvant epirubicin plus docetaxelchemotherapy in stages II and III breast cancer

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Background: This phase III clinical study was designed to investigate whether 6 cycles of epirubicin plus docetaxel (ED) is more effective than 4 cycles of ED as neoadjuvant chemotherapy (NC) in patients with stage II or III breast cancer.

Patients and Methods: Women with breast cancer that had tumors larger than 3 cm were prospectively randomized to receive 4 or 6 cycles of epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 every 3 weeks. The primary end point was the clinical response to NC.

Results: A total of 176 patients were randomly assigned, and 150 patients were assessable for efficacy and toxicity. Groups were well balanced for clinicopathologic parameters. The median age was 42 years (range 30−58). Overall clinical response was observed in 72% with ED4 and 82% with ED6. pCR was observed in 11% with ED4 and in 24% with ED6 ($p = 0.047$). 47% of the ED4 group underwent breast conserving surgery (BCS) whereas 58% of ED6 group underwent BCS. Grade 3/4 neutropenia was observed in 27% in ED4 and 31% in ED6. Febrile neutropenia occurred in 17% with ED4 and 19% with ED6. Grade 3 mucositis was observed in 8% with ED4 and in 6% with ED6.

Conclusion: Six cycles of ED enhanced the rates of pCR and BCS compared with 4 cycles without increasing treatment-related toxicities.

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High pathologic complete remission rate with liposome-encapsulated doxorubicin + paclitaxel + trastuzumab as primary treatment in HER-2 positive operable breast cancer: clinical experience

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Background: The combination of liposome-encapsulated doxorubicin + paclitaxel + trastuzumab is associated with high response rate without risk of clinical congestive heart failure. We present our clinical experience with this combination as primary treatment in HER-2 positive operable breast cancer, describing efficacy and toxicity data.

Material and Methods: Twenty patients with previously untreated HER-2 positive were analysed. Primary treatment consisted of 6 cycles of liposome-encapsulated doxorubicin (50 mg/m^2 3-weekly), paclitaxel (80 mg/m^2/week) and trastuzumab (4 mg/kg loading dose, then 2 mg/kg/week). Tumor response was evaluated with imaging studies after the third cycle and before the surgery. Cardiac evaluation was performed at baseline and repeated after completion of the primary treatment. All patients underwent surgery. Pathologic complete response (pCR) was defined as complete disappearance of all invasive cancer in breast and axilla.

Results: Between August 2008 and October 2009 twenty patients (5 stage IIb, 13 stage IIIa, 3 stage IIIb) completed primary treatment. Median age 47.36 (range 33.4–61.4). All patients achieved clinical response: 11 CR (55%) and 9 PR (45%). 6 patients underwent conservative surgery (33.3%). 14 patients achieved pCR (70%) and in 3 patients rested minimal residual disease (<0.5 cm) (15%). By status hormone receptor (HR) pCR was 4/6 (66.6%) in HR positive and 10/12 (83.3%) in HR negative. All 6 planned cycles of treatment was completed by 17 patients (85%). In terms of toxicity 4 patients had presented one episode of neutropenic fever (20%); none of these patients presented new episodes of neutropenia after the administration of prophylactic granulocyte colony-stimulating factor. Any patient developed congestive heart failure, a decrease between 10−20% in the cardiac ejection fraction, asymptomatic and above normal limit was observed in 5 patients (25%).

Conclusions: These data indicate that the triple combination is very active and safe in the primary treatment of the operable HER-2 positive breast cancer. A phase II study is ongoing.

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Implementation of adjuvant trastuzumab in breast cancer patients in the Netherlands

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Background: Recent studies have shown that trastuzumab combined with adjuvant chemotherapy improves outcome in women with HER2-positive breast cancer. Based on these results, a new national guideline was released in the Netherlands on September 15th 2005 stating that adjuvant chemotherapy should be combined with trastuzumab for women with HER2-positive breast cancer. This study evaluates the implementation of trastuzumab in clinical practice, guideline compliance and regional differences between the eight Comprehensive Cancer Centre regions in the Netherlands.

Methods: All women diagnosed with breast cancer between September 2005 and January 2007 were selected from the population based Netherlands Cancer Registry (NCR), covering all 16.4 million inhabitants. Women without surgery, with metastases at diagnosis or who received neoadjuvant chemotherapy were excluded. HER2 overexpression was recorded in the NCR based on IHC scores or FISH if indicated.

Results: The study included 14,934 patients. Of those, 1,928 (13%) had a tumour which overexpressed HER2. HER2 overexpression decreased with age from 22% in women under 40 years to 9% in women $\geqslant$70 years. Of all 1,928 women with HER2 overexpression, 1,114 (58%) received adjuvant chemotherapy. This percentage decreased from 93% among women <40 years to 8% among women 70−79 years of age. Of 1,585 women <70 years with HER2 overexpression, 1,095 women received adjuvant chemotherapy. Of these, 6% did not receive trastuzumab (regional range: 3−16%, p = 0.001). This percentage decreased from 9% in the first 4 months after release of the new guideline (regional variation 0−24%, p = 0.029) to 3% in the last trimester of 2006 (regional variation 0−12%, p = 0.517). Most common reasons for women not to receive trastuzumab were cardiotoxicity (29%) and patient refusal (21%). In 8% others reasons were given, in 42% no reason was given in the medical chart.

Conclusion: The percentage of women with HER2-positive breast cancer is markedly lower than the assumed 25% in the Netherlands. Of women with HER2 overexpression treated with adjuvant chemotherapy, 6% did not receive trastuzumab. The implementation of trastuzumab in clinical practice was rapid, with significant regional variation. One year after introduction in the guideline, regional differences disappeared. There was a known legitimate reason not to give trastuzumab in 58% of the 61 patients who did not receive trastuzumab.

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A validated analytical method for the simultaneous quantification of tamoxifen, endoxifen, anastrozole and letrozole

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Background: Liquid chromatography hyphenated to tandem mass spectrometry (LC/MS/MS) represents a powerful analytical method for the quantification of drugs in patients. Concerning the endocrine therapy of breast cancer, LC/MS/MS methods have been developed for therapeutic drug monitoring. However, none of the published methods allows for the simultaneous analysis of estrogene receptor antagonists as well as aromatase inhibitors. Thus, our aim was to develop and to validate a LC/MS/MS method covering drugs frequently prescribed in the endocrine therapy of breast cancer (tamoxifen, anastrozole, letrozole) allowing for a convenient pharmacokinetic drug monitoring.

Material and Methods: Blood plasma samples were collected from 320 patients undergoing endocrine breast cancer therapy and stored at −20ºC. To prepare a sample for LC-MS/MS analysis, 1 ml plasma was treated with a solid phase extraction procedure using a cation mixed-mode polymeric sorbent phase (Strata-X-C cartridges, Phenomenex, Torrance, CA). Chromatographic separation was accomplished on a reversed-phase column (200 mm $\times$ 0.5 mm, Eurosphere-C18, 5 μm, Knauer, Berlin) by using a gradient of acetone in an aqueous hexafluorobutyric acid solution. Mass spectrometric detection was performed on a quadrupole-quadrupole-linear ion trap instrument (Q Trap 3200, Applied Biosystems, Foster City, CA).

Results: We have developed a fully validated method for the simultaneous quantitative analysis of tamoxifen, its active metabolite endoxifen, and the non-steroidal aromatase inhibitors anastrozole and letrozole in human plasma. Validation was accomplished according to published guidelines [1] for a concentration range of 25–500 ng/ml for tamoxifen, 10–200 ng/ml for endoxifen, 5–200 ng/ml for anastrozol and 10–300 ng/ml for letrozol. The applicability of the method has been demonstrated by analyzing plasma samples of 320 patients treated with tamoxifen, anastrozole and letrozole.

Conclusion: The developed method represents a reliable and convenient tool for the simultaneous quantitative analysis of tamoxifen/endoxifen, anastrozol and letrozole allowing for convenient pharmacokinetic drug monitoring in the endocrine therapy of breast cancer.

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Adjuvant endocrine therapy in premenopausal women − toxicities and adherence rates from a tertiary care centre

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Background: Multiple randomized trials have demonstrated the efficacy of aromatase inhibitors (AIs) in postmenopausal women with hormone receptor positive (HR+) early-stage breast cancer (EBC). Ongoing clinical trials are examining the role of AIs given concurrently with ovarian suppression (OS) in premenopausal women with HR+ EBC. This study reports on toxicities and adherence rates observed in premenopausal women treated with OS and tamoxifen (Tam)/AIs in an academic cancer centre.

Material and Methods: Premenopausal women with HR+ EBC were identified through a home LHRH antagonist injection registry from Jan/05 to May/09. Data collected included: demographics, treatments, choices of endocrine therapies, treatment toxicities and adherence rates.

Results: 84 eligible patients (pts) were evaluated. Median age at diagnosis was 44 years (range: 24−53). Stage was I/II/III in 14/47/23 pts and 32 (38%) pts had her2/neu positive disease. Median BMI was 25.6. The majority of pts (90%) received chemotherapy. Initial endocrine therapy choices included Tam alone/AI+ OS/Tam+OS in 14/62/8 pts. Of the Tam alone group, 93% of pts switched to AI+OS and 7% switched to Tam+OS. The AI+OS group had 90% adherence rate at the time of evaluation. Few pts switched from AI+OS to Tam (1.6%) and Tam+OS (4.8%). Most pts (19/23) with stage III stage were on AI+OS. 79 pts had evaluations on BMD with 33 pts having follow-up BMD studies. 44% pts proceeded to have bilateral oophrectomy. Common toxicities for pts on AI+OS were arthralgia/myalgia (40%), hot flushes (35%), fatigue (19%), vaginal symptoms (18%), weight gain (15%), sleep disturbances (10%) and psychosocial issues (7%).

Conclusion: The use of AI+OS is not the current standard hormonal treatment in premenopausal women with HR+ EBC. In our experience, it is unclear if this choice has been driven by patient choice or physician advice. The 90% adherence rate in AI+OS group seems to be higher than the clinically observed AI adherence rates in postmenopausal women despite significant toxicities from treatment. Survivorship issues are complex in premenopausal woman and require careful attention and standardized approach.

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Actual or adjusted surface area: which should we use?

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Background: Calculation of chemotherapeutic drugs doses was standardized to Body Surface Area, with the aim to produce optimum systemic drug level & minimize drug toxicity; it also can be very challenging in obese cancer patients. Obesity represents a condition of excessive adipose tissue with its currently accepted definition is defined as Body Mass Index >30 kg/m^2); it once believed that obese patients who received chemotherapy on their actual body weight would result in increased toxicity, secondary to distribution of lipid soluble drugs into the adipose tissue. By using Adjusted Body Weight it's assumed that cancer patients would receive a dose of a particular cytotoxic drug associated with an acceptable degree of toxicity without reducing its therapeutic effect. The aim of this study is considering the use of adjusted body weight for calculation of chemotherapeutic drugs