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Luteal versus follicular phase surgical oophorectomy plus tamoxifen in premenopausal women with metastatic hormone receptor positive breast cancer

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Conflict of interest statement

The authors indicated no potential conflicts of interest.

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Abstract

Purpose—In premenopausal women with metastatic hormone receptor positive breast cancer, hormonal therapy is the first line therapy. GnRH + tamoxifen therapies have been found to be more effective. The pattern of recurrence risk over time after primary surgery suggests that peri-operative factors impact recurrence. Secondary analyses of an adjuvant trial suggested that the luteal phase timing of surgical oophorectomy in the menstrual cycle simultaneous with primary breast surgery favorably influenced long-term outcomes.

Methods—249 premenopausal women with incurable or metastatic hormone receptor positive breast cancer entered a trial in which they were randomized to historical mid-luteal or mid-follicular phase surgical oophorectomy followed by oral tamoxifen treatment. Kaplan-Meier methods, the log-rank test, and multivariable Cox regression models were used to assess overall and progression free survival in the two randomized groups and by hormone confirmed menstrual cycle phase.

Results—Overall survival (OS) and progression-free survival were not demonstrated to be different in the two randomized groups. In a secondary analysis, OS appeared worse in luteal phase surgery patients with progesterone levels of <2ng/ml (anovulatory patients) (adjusted hazard ratio 1.46, 95% CI: 0.89–2.41, $p=0.14$) compared to patients in luteal phase with progesterone 2ng/ml or higher. Median overall survival was 2.0 years (95% CI: 1.7 – 2.3) and OS at 4 years was 26%.

Conclusions—The history-based timing of surgical oophorectomy in the menstrual cycle did not influence outcomes in this trial of metastatic patients.

[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00293540) number NCT 00293540

Keywords

oophorectomy; metastatic; anovulatory; acute-effects

Background

In premenopausal women with hormone receptor-positive metastatic breast cancer, hormonal therapy is the first-line therapy^{1,2}. For many years tamoxifen alone, gonadotropin-releasing hormone (GnRH) analogue treatment, or oophorectomy (usually by surgery) had been considered equivalent and the interventions of choice^{3–5}. A decade ago three separate studies and a meta-analysis of these three studies plus a fourth, found that patients with recurrent disease who are not currently taking tamoxifen, combined hormonal therapy with a GnRH analogue and tamoxifen was better than GnRH treatment^{6–9} or tamoxifen alone⁸ for overall survival. Because of the costs associated with GnRH treatment, surgical oophorectomy is the more cost-effective intervention for the majority of women globally

eligible for such intervention, most of whom now come from low- and middle-income countries.

For many years it has been clear that primary breast surgery peri-operative factors must impact recurrence: the pattern of recurrence risk is characterized by a peak at about three years from primary treatment¹⁰. Baum et al posited a mathematical model to better explain patterns and inconsistencies in recurrence, a model they found “exquisitely sensitive” to peri-operative variables¹¹. In secondary exploratory analysis of an adjuvant trial of surgical oophorectomy and tamoxifen in 709 Vietnamese and Chinese women, adjuvantly-treated women were suggested to have markedly better disease-free (DFS) and overall survival (OS) if the oophorectomy surgery was done in the history-estimated luteal phase of the menstrual cycle¹². Because in this study patients treated with only breast surgery demonstrated no differences in outcomes based on menstrual cycle history, we suggested that peri-operative factors associated with the ovarian surgery could explain these differences. We thus expanded the focus to peri-operative biology regardless of specific type. Oophorectomy surgery done simultaneously with primary surgery is associated with markedly different hormonal levels according to the time this is done in the menstrual cycle, particularly of progesterone which is essentially absent in the follicular phase, while exhibiting concentrations 20-fold those of estradiol in the luteal phase. For patients who do not undergo a regular menstrual cycle at the time of surgical oophorectomy, the hormonal conditions over days which precede this surgery may impact also various biological processes and tumor populations. These circumstances suggest that particularly for hormonally sensitive tumors such as breast cancers, differences in the hormonal milieu and abrupt changes in this that occur with surgical oophorectomy might acutely and differentially impact micro-metastatic disease, in the same way that orchiectomy produces acute symptomatic benefit in patients with metastatic prostate cancer. Since progression of disease and survival with established metastatic disease are dependent on development of new metastases as well as growth of evident lesions, we assessed that it was reasonable to assess whether luteal phase oophorectomy combined with tamoxifen is significantly more beneficial than follicular phase oophorectomy and tamoxifen both in the adjuvant setting and in women with newly diagnosed metastatic breast cancer. We have reported our adjuvant randomized trial results showing that although progesterone status at oophorectomy is associated with recurrence risk¹³, timing of surgery during a history-estimated luteal phase showed no detectable survival benefit, which seemed to be explained by large variability in progesterone levels. In the following report, we describe results of a randomized trial of oophorectomy in the history estimated mid-luteal or mid-follicular phase of the menstrual cycle in women with metastatic breast cancer, with the vast majority followed for two years or until the time of her death. The results in the adjuvant trial generated hypotheses about benefits of the timing of surgery and progesterone levels, and this prompted us, as we had planned, to independently test these further with blood progesterone levels obtained on the day of oophorectomy in this metastatic trial.

Methods

Design and Eligibility

Between August, 2004 and October, 2011, at 23 clinical sites in Bangladesh, The Philippines, China, Nigeria, Indonesia, Malaysia, Taiwan, Morocco and Vietnam we recruited 249 premenopausal women with hormone receptor positive (estrogen receptor and/or progesterone receptor positive in local laboratories by immuno-histochemical assays), in common clinical circumstances in that they had invasive and incurable or metastatic breast cancers. All subjects were candidates for treatment with surgical oophorectomy and tamoxifen or oophorectomy alone. Incurable disease was defined as those patients with stage III N2 or N3 disease who were not operable for cure. At registration, on study eligible patients were randomized to receive surgical oophorectomy during the next history-estimated mid-luteal phase of the menstrual cycle (5–9 days before the expected first day of the next menstrual cycle) OR surgical oophorectomy during the next history-estimated mid-follicular phase of the menstrual cycle (3–7 days before the estimated last day of the follicular phase of the cycle). In each patient, the assigned surgery dates were based on that individual patient's reported menstrual cycle length and the assumption that luteal phase would occur in the last 14 days of the menstrual cycle. We used history-estimated timing because this trial was designed to test the benefit of a pragmatic protocol in which history could be used for a decision about timing of surgery.

The study was approved at individual institutions in each participating country and/or by supervising in-country Institutional Review Boards (IRBs) for these institutions and at lead investigator's American institutions, initially the University of Wisconsin, later at Ohio State University, and finally with the Western IRB. Annual written re-approvals by all IRBs were also obtained. All participants provided written informed consent. All of the participating institutions and IRBs were registered with the Office for Human Subjects' Protection (OHRP) in the United States. A data and safety monitoring committee of 6 individuals approved by the United States National Institutes of Health reviewed the trial conduct, primary, secondary and safety results annually. The trial was registered at ClinicalTrials.gov number, NCT 00293540 on September 12, 2005.

Eligibility criteria for the trial included: age 18 and older; history of menstrual cycles for the last three months of 25–35 days (inclusive) and last menstrual period < 35 days ago; pathological diagnosis of invasive breast cancer which was estrogen and or progesterone receptor positive by local laboratory standards from examinations of the primary tumor or metastatic tumor tissues; clear clinical evidence of previously untreated and/or new distant metastatic disease or of surgically incurable inoperable loco-regional disease; absence of life-threatening metastatic disease involving the CNS, lung (with extensive lymphangitic), or liver, evaluated respectively by symptom review, chest x-ray and liver ultrasound studies; negative HCG pregnancy test within the last 14 days; normal bilirubin, serum creatinine and calcium levels by local laboratory standards; not using oral contraceptives; candidate for surgical oophorectomy; available for follow up assessments; and able to and providing written informed consent. Patients who had previously been treated with tamoxifen were study eligible if their circumstances suggested that further hormonal therapy was a

reasonable therapeutic choice. Patients who had had previous primary treatment and adjuvant therapies had to now have evidence of incurable and or metastatic disease to be study eligible. Patients who had had a previous lumpectomy without a pathological diagnosis or further treatment, were study eligible if they had demonstrable incurable or metastatic pathologically confirmed disease. In sum the study population was pragmatically defined by their disease incurable status, and appropriateness for the study treatment.

Treatment

Participating institutions and investigators agreed to make every effort to perform surgical oophorectomy within the randomly assigned time window. Patients who were not taking tamoxifen at the time of their registration on study and who had not taken this medication in the last 6 months were started on tamoxifen 20 mg daily. Patients on tamoxifen at diagnosis of metastatic disease had this medication stopped. Tamoxifen (20 mg) tablets were provided to all tamoxifen-eligible participants and begun within 6 days of surgery where indicated. When progressive disease developed in study patients and tamoxifen was being taken, it was to be stopped. If a response to the study treatment was adjudged to have occurred, new hormonal therapy was recommended. In many sites, options for additional therapy were limited because of economic considerations or patient preferences.

Laboratory studies

On the day of patient surgeries 10ml of blood was drawn prior to any anesthesia or drugs and three hours after the second ovarian artery was ligated and the sera was separated and frozen. At later dates, in batches, without any episodes of thawing, the serum specimens for all but the Chinese sites were shipped frozen to the investigators' US institution sample bank. One-hundred and thirty three serum progesterone values were determined using an enzyme immunoassay modified from Munro et al.¹⁴ and further modified from Saltzman et al.¹⁵. Forty-one serum progesterone levels from the Chinese sites were analyzed in country by standard laboratory methods.

Quality Control

Initially, case report forms were used to gather study data completed by clinical site investigator teams. After the initial three years of the study, all case data were entered by site investigators into a secure web-based system. During audits, monitors sought to verify key treatment, safety and efficacy data against study on-site paper and hospital records. Annual data and safety monitoring committee meetings reviewed detailed study data reports, particularly on treatment compliance and adverse events.

Randomization procedure

Eligible patients were randomized in a 1:1 ratio to surgical oophorectomy in the history estimated mid-luteal phase or mid-follicular phase of the menstrual cycle. Computer generated randomization assignment, monitored and implemented centrally through the data coordination center in the U.S., was blocked in allocation and was stratified only by site.

Statistical methods

Sample size and interim analysis—Based on data from previous reports^{6–9,12} this trial was designed to detect a hazard ratio (HR) for overall survival of 0.67 in favor of the luteal phase surgery group, assuming a (two-sided) type I error of 0.05 and 80% power, with 2.5 years median survival in the follicular phase surgery group. These initial calculations assumed an accrual period of approximately 3 years with 2.5–3 years of additional follow up. It was expected that 350 patients would be accrued to achieve approximately 198 total events (deaths) during the trial.

By the summer of 2011 after 7 years of recruitment and slowing accrual, an interim analysis was performed in cooperation with the trial Data and Safety Monitoring Committee (DSMC) to determine if recruitment to the trial should be continued. The interim analysis plan, which was provided to the DSMC and approved before analysis, consisted of calculating conditional power (CP) to inform this decision. Conditional power was to be calculated for the total number of expected events (198 events) for the estimated effect size at the interim analysis time and under the originally proposed effect size through the end of August 2011^{16–18}. The interim analysis plan stated that if the conditional power, for 198 events was less than 50%, patient accrual would be stopped. No test for efficacy or increase in sample size was included in the plan.

Making the assumption that the effect size at the time of the interim analysis was true (August 2011 with 2/3 of 198 events observed), produced a conditional power, for the full 198 events of 27%. Given these results, trial accrual was discontinued and patients already enrolled were followed through March 2014¹⁹, so that each patient had a minimum of 2.5 years of follow-up.

Analyses—Overall survival (OS) and progression free survival (PFS) curves were calculated using Kaplan-Meier methods²⁰, and the differences in survival curves were assessed via the log-rank test²¹. The planned primary hypothesis test compared OS between the randomized groups by the log-rank test. Confidence intervals for median survival estimates were calculated using the log-log method. The Cox proportional hazards model²² was used to estimate univariable hazard ratios and multivariable Cox models were used to estimate adjusted hazard ratios (aHR). Adjustment factors were included based on known prior relationships with progression or survival. The assumption of proportional hazards was verified by tests and plots of the scaled Schoenfeld residuals²³. For patients who had been previously diagnosed and treated, the disease-free interval was defined as the time from the initial diagnosis of disease to the time of the first recurrence or metastasis.

In our adjuvant trial, we found that confirmed follicular surgery patients had better survival than confirmed or unconfirmed luteal patients, and that unconfirmed luteal patients showed substantially worse survival than confirmed luteal patients¹³. Based on these specific results and previously specified secondary plans to explore hormonal classification of patients, we planned to test these two hypotheses in this metastatic trial. Metastatic patients were categorized using both historical and hormone level information into three groups with a normal follicular phase defined to be a maximum of 14 days¹³. This procedure allows for the investigation of the impact of variability of follicular phase duration. These three groups

were: patients in historical follicular phase (day 14 or before of the menstrual cycle) with progesterone levels <2ng/ml (confirmed follicular); patients in historical luteal phase (beyond day 14 of the menstrual cycle) with progesterone levels 2ng/ml or greater (confirmed luteal); and patients in historical luteal phase with progesterone levels <2ng/ml (unconfirmed luteal). The unconfirmed luteal group patients were considered anovulatory at the time they underwent their oophorectomy surgeries.

OS was defined as the time from randomization to the date of death or to the censoring date for last follow-up when the patient was known to be alive. PFS was defined as the time from the date of randomization to the date of first documentation of progressive disease or death. Patients without progression or death were censored at the date of their last follow-up. In all comparisons of the randomized patients, treatment group assigned at randomization was compared, regardless of the treatment received. Exploratory analyses were used to explain the primary findings. P-values in exploratory analyses were reported for completeness, were not corrected for multiplicity, and cannot be interpreted as formal hypothesis tests. All analyses were conducted in SAS v9.3 (SAS Institute, Cary, NC) and Stata v10.1 (StataCorp, College Station, TX).

Role of the funding sources

The sponsors had no roles in the implementation, conduct, analysis and interpretation of the study after agreeing to provide the funding.

Results

Following the results from interim analysis, trial accrual was halted in October 2011, when 249 patients had been consented and registered to the trial. Accrual by (number of sites) and country was as follows: Bangladesh (4): 101 patients; Philippines (5) 55 patients; China (7) 57 patients; Nigeria (1) 14 patients; Indonesia (1) 7 patients; Malaysia (1) 6 patients; Taiwan (2) 7 patients; Morocco (1) 1 patient; and Vietnam (1) 1 patient. The numbers of patients assigned to each randomized treatment group, who were ineligible or who did not receive surgery are summarized in Figure 1. Two patients were determined to be ineligible after randomization (one patient was pregnant and one patient had unconfirmed metastatic disease). Of the twelve who did not receive surgery, eight refused or withdrew prior to surgery.

Table 1 describes patient characteristics by treatment group. Of the 234 patients in the primary analysis dataset, 211 (90.2%) received their assigned treatment during the 5-day treatment windows. Patients assigned to mid-follicular phase surgery had a higher rate of prior treatment (50% vs. 38% in the mid-luteal phase group), less frequently had viscera as a dominant metastatic site (9% vs. 17% in the mid-luteal phase group), and more frequently had progesterone receptor negative tumors (10% vs. 0%). Progesterone levels were on average: 3.5 ng/ml (sd=5.4) for the mid-luteal phase group and 2.1 ng/ml (sd=3.9) for the mid-follicular phase group. In patients assigned to mid-luteal phase surgery, only 37% had progesterone levels of 2 ng/ml or greater. Fifteen patients had had prior tamoxifen treatment and were on tamoxifen which was stopped at the time they developed metastatic disease and were entered on this study. Her-2/neu IHC assessments were not available on these patients

at baseline and data on the presence of multi-site metastatic disease and surgical margin data for patients who underwent concurrent mastectomy were incomplete and unreliable. In the country accruing the most patients, Bangladesh, 75 of 97 operated patients had concurrent oophorectomy and mastectomy. Rigorous assessment of the impact of this additional primary tumor surgery was not possible.

Completeness of follow up information

Of the 234 patients in the primary analysis set, 229 (97.9%) had follow-up out to at least 2 years or to death.

Adverse events—One patient developed deep vein thrombosis and was treated successfully with anti-coagulants. Three surgically treated patients died within 30 days of surgery. On review, while the stresses of surgery probably contributed to each of these deaths, complications of metastatic disease appeared to be the primary causes of death.

The current report is based on evaluations to March 2014. As of this time, the median follow up for patients who were still alive was 4.0 years and a total of 178 deaths had been observed. Four deaths were due to causes other than progressive metastatic disease.

Primary hypothesis testing—Based on the primary analysis data set, described in Figure 1, median overall survival in the mid-luteal phase group was 2.14 years (95% CI: 1.53 – 2.67) and 2.00 years (95% CI: 1.61–2.31) for the mid-follicular phase group (Unadjusted Cox HR=0.87, 95% CI: 0.65–1.17, log-rank test $p=0.36$) (Figure 2) (combined groups' median OS: 2.04 years, 95% CI: 1.74–2.31). Multivariable Cox models, adjusted for known prognostic variables including performance status at baseline, age, prior treatment, disease-free interval and dominant metastatic site, did not substantially alter this effect (Table 2) (aHR: 0.80, 95% CI: 0.59–1.10). Older patients (1-year increase aHR = 0.97, 95% CI: 0.95–1.00, $p=0.05$) and those with performance status of 0 compared to greater than 0 (aHR: 1.51, 95% CI: 1.07–2.13, $p=0.02$) exhibited better OS. Additionally, the interaction between prior therapy and randomized group was explored. The observed aHR for mid-luteal vs. mid-follicular was 0.62 (95% CI: 0.38–1.02) for those with prior therapy and 0.95 (95% CI: 0.63–1.43) for those without. No statistically significant interaction was observed ($p=0.19$), however this study is not designed to adequately assess the interaction question.

Comparison of PFS between randomized groups did not indicate a benefit of mid-luteal phase surgery. Median progression free survival for mid-luteal phase surgery was 0.72 years (95% CI: 0.57 – 1.18) and for the mid-follicular phase group was 0.91 years (95% CI: 0.70 – 1.15) (HR = 1.05 (95% CI: 0.79 – 1.38), log-rank $p=0.76$). A total of 98 mid-luteal phase patients and 97 mid-follicular phase patients experienced PFS events over the course of follow-up. The median PFS across both groups was 0.84 years (95% CI: 0.67–1.07). In multivariable Cox models, the adjusted hazard ratio (including the same covariates as in the models for OS) comparing mid-luteal phase surgery to mid-follicular phase surgery was very similar to the unadjusted estimate (aHR: 1.01, 95% CI: 0.75–1.36, $p=0.95$). Neither models for OS or PFS indicated violation of the proportional hazards assumption.

Secondary analyses based on two prior generated hypotheses

Classification of patients by blood hormone progesterone level on the day of surgery and menstrual cycle history was possible for 166 patients. Twelve patients operated on during historical follicular phase had progesterone levels 2ng/ml or greater; these patients were omitted from this analysis. The remaining 154 cases were classified into three groups: confirmed follicular, confirmed luteal, and unconfirmed luteal as defined above. Note that despite screening for regular menstrual cyclicity during the prior three months, 61% of the women randomized to history-determined luteal phase surgery had pg levels < 2ng/ml. The mean and standard deviation of pg levels in those randomized to luteal phase showed much more variation and lower levels than expected. Figure 3 and Table 3 describe overall survival for these three groups. First, we did not corroborate our exploratory findings in the adjuvant trial on the superiority of confirmed follicular surgery as compared to confirmed luteal. However we did find that patients in the history estimated luteal phase with low progesterone levels and presumably anovulatory (<2 ng/ml), those denoted as unconfirmed luteal, appeared to show worse overall survival (aHR 1.46, 95% CI: 0.89–2.41, p=0.14) compared to patients in the history estimated luteal phase with progesterone 2ng/ml or higher. Confirmed luteal patients were slightly older (40.3 vs. 38.6 years), had longer disease-free intervals (22% vs. 12% for interval of at least one year), and lower performance status (62% vs. 71% with a status of zero) than unconfirmed luteal patients. Analyses of PFS in these three groups showed similar patterns.

Patients with viscera as the dominant metastatic site had worse survival than those with only soft tissue metastases (aHR: 2.05, 95% CI: 1.13–3.74, p=0.02).

Discussion

Results from this pragmatic randomized trial of history estimated mid-luteal phase versus mid-follicular phase oophorectomy, have shown that this trial was properly conducted. Our experience provides evidence that multicenter international trials, including non-high-income countries, can be successfully pursued, perhaps particularly when they are designed to evaluate an intervention in a practical setting. While some additional detailed information (for example: the number of patients who had concurrent mastectomy) would have further enriched the analyses, the breadth of data collected in this study from mostly very poor patients from 23 sites in 9 countries supports designing practical trials similar to this one. While data on concurrent mastectomy would have provided additional analytic possibilities, the current assessment is that such procedures are of uncertain benefit (nccn.com, Breast Cancer Treatment Guidelines, accessed August, 2015).

The observed overall median survival of 24 months in this trial is 9 months less than has been seen in Western population studies. Younger age, multiple co-morbidities, limited availability and use of secondary therapies, and more advanced-bulky disease at treatment, are likely to account for this difference. It is notable that 4-year OS was 26% indicating long-term disease control in these patients. For clinicians in the participating countries where the majority of breast cancer patients are premenopausal and present with incurable disease, these results are an important demonstration of the usefulness of this practical combined hormonal therapy. When appropriate care is taken of the biopsied tissues, the

frequencies of hormone receptor positive tumors are similar in high income and low and middle income countries²⁴.

The most important results however, in the contexts of our adjuvant study results showing that anovulatory patients did poorly and to those results of Badwe (where progesterone supplemented patients did well) is that the current data are again suggesting that patients who are in historical luteal phase with low progesterone levels (anovulatory patients) at the time of treatment, have worse survival^{13,25}. First, it is important to be clear that the investigators believed all of these patients to be having regular menstrual cycles, but 59/96 (61%) of patients in historical luteal phase (here defined as at least 14 days after the start of the current menstrual cycle), had low progesterone levels. The median survival in these anovulatory patients was 18 months, nearly a year shorter than the 28 month median survival in confirmed luteal or confirmed follicular phase patients. The problem of accurately assessing menstrual cycle status based on history alone was also observed in the North American NCCTG adjuvant study conducted during the same era²⁶. What mechanisms might explain these findings? Both this and our adjuvant study could be seen as ones in which a period of high estradiol (E2) (a couple of weeks at least) and no progesterone elevation, followed by oophorectomy with abrupt lowering of E2 and no progesterone rise, occurred in patients prior to the time of oophorectomy. It may be the last (prolonged) hormonal signal which is important, accompanied by a no-progesterone rise signal, because of oophorectomy. The circulating tumor cells from the mastectomy surgeries in both the adjuvant and metastatic studies surgery, stromal cells around metastases, or metastatic populations could be affected. The important matter appears to be that acute signaling at this operative time appears to result in long-term effects, corresponding to the suggestion made in Baum's mathematical model¹¹. This would seem to be not so much different from the immediate response to orchiectomy seen in metastatic prostate cancer, but not a model (i.e. with acute effects) that has been considered with oophorectomy. Biologically, we could consider this to be the opposite of what Badwe et al. did, where with a depot progesterone injection they created a high progesterone environment pre- and peri-operatively, which was associated with long term benefits in the highest risk, axillary node positive, patients.²⁵

Application in clinical practice

Given the high frequency of peri-menopausal status found by hormone assessments among the patients in our two and other studies, progesterone level determination may be helpful in differentiating prognosis²⁶. In particular we can speculate that when surgical oophorectomy is the planned intervention, if the patient's history suggests she is in luteal phase, but the progesterone level is low, oophorectomy should not be done at this time or progesterone should be administered as in Badwe. For large numbers of women in low and middle income countries these provocative results are relevant and should be considered. Further this study, our adjuvant study and the results of Badwe's study suggest that peri-operative biology is important in impacting long term outcomes in breast cancer, which observation warrants further investigation in breast cancer and for other solid tumors. However unobserved differences between the women in these groups, beyond the ones we adjusted for in the multivariable analysis, might explain these results, but these differences would somehow have occurred in both of our trials¹³.

Conclusion

The timing of surgical oophorectomy treatment in the menstrual cycle in premenopausal patients with metastatic or incurable hormone receptor positive breast cancer did not show a significant impact on long term survival. A high fraction of such patients in historical luteal phase had low progesterone levels suggesting they were anovulatory during the specific cycle.

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Highlights

- Surgical oophorectomy + tamoxifen is good therapy in patients with limited resources.
- Menstrual cycle histories are inaccurate because of long follicular phases.
- Patients with long follicular phases tend to have poorer survival with oophorectomy.
- With other data, this study suggests peri-operative adverse effects in some patients.

Figure 1.
CONSORT diagram

Figure 2. Kaplan-Meier curves for OS by randomized group (A- luteal phase surgery, B-follicular phase surgery). Number at risk indicated with events in parentheses. Log-rank $p=0.36$ and unadjusted Cox HR=0.87 (95% CI: 0.65–1.17).

Figure 3. Kaplan-Meier curves for OS for 154 cases categorized by menstrual cycle history and progesterone levels on the day of oophorectomy surgery (conf foll – confirmed follicular, conf lut – confirmed luteal, unconf lut – unconfirmed luteal)

Table 1

Demographic and clinical characteristics of study patients included in primary analysis (Group A – luteal phase surgery, Group B – follicular phase surgery). Note that not all patients had complete data.

Variable	Level	Group A-Luteal (n=115)	Group B-Follicular (n=119)	Total
Treatment status	No treatment	4 (3.5%)	8 (6.7%)	12 (5.1%)
	Treatment received inside assigned window	104 (90.4%)	107 (89.9%)	211 (90.2%)
	Treatment received outside assigned window	7 (6.1%)	4 (3.4%)	11 (4.7%)
Dominant metastatic site	Soft tissue	76 (66.1%)	83 (69.7%)	159 (67.9%)
	Bone	20 (17.4%)	25 (21.0%)	45 (19.2%)
	Viscera	19 (16.5%)	11 (9.2%)	30 (12.8%)
Age (years)	Mean (SD)	39.0 (5.4)	38.6 (5.7)	38.8 (5.6)
Menstrual cycle length (days)	Mean (SD)	29.5 (2.2)	29.9 (2.2)	29.7 (2.2)
Day of menstrual cycle surgery conducted	Mean (SD)	23.3 (2.7)	11.4 (2.7)	17.3 (6.5)
Phase of surgery by menstrual cycle history	Follicular	0 (0.0%)	91 (85.8%)	91 (42.9%)
	Luteal	106 (100%)	15 (14.2%)	121 (57.1%)
Body mass index (kg/m ²)	Mean (SD)	23.6 (3.7)	23.2 (4.4)	23.4 (4.0)
Performance status	Fully active	77 (69.4%)	80 (70.8%)	157 (70.1%)
	Symptoms but ambulatory	30 (27.0%)	29 (25.7%)	59 (26.3%)
	No work but self-care	2 (1.8%)	3 (2.7%)	5 (2.2%)
	Limited self-care	2 (1.8%)	1 (0.9%)	3 (1.3%)
ER status	Negative	8 (7.0%)	0 (0.0%)	8 (3.4%)
	Positive	106 (93.0%)	118 (100%)	224 (96.6%)
PR status	Negative	2 (1.8%)	12 (10.5%)	14 (6.3%)
	Positive	108 (98.2%)	102 (89.5%)	210 (93.8%)
Treatment for disease prior to entry on study	No	69 (62.2%)	57 (50.0%)	126 (56.0%)
	Yes	42 (37.8%)	57 (50.0%)	99 (44.0%)
Prior treatment – lumpectomy	No	98 (88.3%)	98 (86.0%)	196 (87.1%)
	Yes	13 (11.7%)	16 (14.0%)	29 (12.9%)
Prior treatment – mastectomy	No	81 (73.0%)	73 (64.0%)	154 (68.4%)
	Yes	30 (27.0%)	41 (36.0%)	71 (31.6%)
Prior treatment – adjuvant chemotherapy	No	90 (81.1%)	87 (76.3%)	177 (78.7%)
	Yes	21 (18.9%)	27 (23.7%)	48 (21.3%)
Prior treatment – adjuvant hormonal therapy	No	98 (88.3%)	99 (86.8%)	197 (87.6%)
	Yes	13 (11.7%)	15 (13.2%)	28 (12.4%)
Prior treatment – radiation	No	104 (93.7%)	100 (87.7%)	204 (90.7%)
	Yes	7 (6.3%)	14 (12.3%)	21 (9.3%)
Eligible for tamoxifen	No	5 (4.6%)	10 (8.8%)	15 (6.8%)
	Yes	104 (95.4%)	103 (91.2%)	207 (93.2%)

Variable	Level	Group A-Luteal (n=115)	Group B-Follicular (n=119)	Total
Progesterone $\geq$ 2 ng/ml	No	56 (62.9%)	69 (81.2%)	125 (71.8%)
	Yes	33 (37.1%)	16 (18.8%)	49 (28.2%)
Progesterone (ng/ml)	Mean (SD)	3.5 (5.4)	2.1 (3.9)	2.8 (4.8)
Confirmed follicular, unconfirmed follicular, confirmed luteal, or unconfirmed luteal	Conf foll	0 (0.0%)	58 (71.6%)	58 (34.9%)
	Unconf foll	0 (0.0%)	12 (14.8%)	12 (7.2%)
	Conf lut	33 (38.8%)	4 (4.9%)	37 (22.3%)
	Unconf lut	52 (61.2%)	7 (8.6%)	59 (35.5%)
Disease-free interval category	None	70 (63.1%)	74 (64.9%)	144 (64.0%)
	< 1 year	22 (19.8%)	16 (14.0%)	38 (16.9%)
	1 year	19 (17.1%)	24 (21.1%)	43 (19.1%)

Table 2

Multivariable Cox model results for OS comparing randomized groups (A-luteal phase surgery, B-follicular phase surgery, n=224)

Variable	HR (95% CI)	p-value
A-luteal vs. B-follicular	0.80 (0.59, 1.10)	0.17
Dominant metastatic site: bone vs. soft tissue	1.05 (0.66, 1.66)	0.84
Dominant metastatic site: viscera vs. soft tissue	1.32 (0.81, 2.15)	0.26
Prior treatment: Yes vs. no	0.90 (0.63, 1.28)	0.55
Performance status > 0 vs. 0	1.51 (1.07, 2.13)	0.019
Age (1-yr increase)	0.97 (0.95, 1.00)	0.050
Disease-free interval: < 1 year vs. none	0.81 (0.50, 1.32)	0.40
Disease-free interval: 1 year vs. none	0.79 (0.50, 1.27)	0.34

Table 3

Multivariable Cox model results for OS comparing patients categorized by history and progesterone levels on day of oophorectomy as confirmed follicular, confirmed luteal or unconfirmed luteal phase (n=153).

Variable	HR (95% CI)	p-value
Confirmed follicular vs. confirmed luteal	1.29 (0.77, 2.14)	0.33
Unconfirmed luteal vs. confirmed luteal	1.46 (0.89, 2.41)	0.14
Dominant metastatic site: bone vs. soft tissue	1.42 (0.82, 2.47)	0.2156
Dominant metastatic site: viscera vs. soft tissue	2.05 (1.13, 3.74)	0.0189
Prior treatment: Yes vs. no	0.82 (0.54, 1.24)	0.3531
Performance status > 0 vs. 0	1.48 (0.97, 2.25)	0.0671
Age (1-yr increase)	0.98 (0.94, 1.01)	0.1647
Disease-free interval: < 1 year vs. none	0.76 (0.44, 1.29)	0.3030
Disease-free interval: 1 year vs. none	0.56 (0.30, 1.02)	0.0583