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Research Article

Surgical Oophorectomy is Ineffective Therapy in Women with Hormone-Receptor Positive Breast Cancer Who are in Historical, but Low-Progesterone Luteal Phase

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Abstract

The hormonal biology of the menstrual cycle has major relevance in the treatment of hormone-sensitive breast cancer. There are 500,000 new cases of hormone-receptor positive breast cancer in premenopausal women annually; 80% of these are among women in low - and middle-income countries. Surgical oophorectomy should play a major role in the treatment of these women. New data from two phase III clinical trials show that women who are in historical luteal phase, but have low progesterone levels at the times of their oophorectomy surgeries benefit little from this intervention. The unique sequence of hormonal signaling to micro-metastases which occurs in this situation offers a logical explanation for this observation. Because surgical oophorectomy is a safe and widely practical and affordable intervention, this new observation and explanation deserves the attention of the practicing global surgical community. Universal application of surgical oophorectomy treatment could save 100,000 lives of young women with breast cancer each year.

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Introduction

Globally each year there are 500,000 premenopausal women with new cases of hormone receptor positive breast cancer. What fraction of these women who present with stage III regionally advanced/ incurable and stage IV disease is unknown. Part of the explanation for late presentations is pubic belief that affordable and practical treatments are unavailable [1]. For women with operable disease, particularly patients with positive axillary nodes and larger tumors, fully an additional one third will survive alive for ten years with optimal adjuvant hormonal therapy such as surgical oophorectomy + tamoxifen (for 5 years), but probably only 25% of women in low- and middle-income (LMIC) countries (which account for 400,000 cases annually) get any such effective adjuvant treatment [2, 3]. Combined ovarian-function targeting (Luteinizing-hormone-releasing hormone-LHRH agonist or surgical oophorectomy- SO) and endocrine -- tamoxifen(T) or aromatase inhibitor treatments-- are more effective than single hormonal treatments alone [3]. For 25 years in multiple clinical trials in the United States and Europe, LHRH and surgical oophorectomy treatments have been considered equivalent in efficacy [4-8]. Putting these observations and data together: if women knew that they could actually get affordable treatment which might save their lives, and if then practitioners worldwide provided this surgical oophorectomy affordable and effective treatment, instead of the 25% of women with this type of disease in LMIC now who die unnecessarily, if essentially all presentations were of operable disease, 100,000 women per year could be saved. The barriers to widespread treatment with surgical oophorectomy plus tamoxifen are beliefs that:

1. LHRH + Aromatase inhibitor treatment is more effective and perhaps safer [6];

2. The data about surgical oophorectomy are limited; and

3. The only appropriate biologic model for hormonal control is a chronic one, focusing on long-term suppression of growth stimulation.

The current communication argues that in fact all three of these beliefs are challengeable. Further, because the Institute of Medicine in the United States has suggested that the quality of care of a medical intervention should be determined through multiple assessments of efficacy, safety, cost-effectiveness and value, patient centeredness, timeliness and equity, this communication argues that using such multiple metrics to evaluate these treatments, leads to a conclusion that surgical oophorectomy plus tamoxifen is superior [9]. The central biologic issue concerning efficacy of surgical oophorectomy relates to evidence that low-progesterone, history-only characterized menstrual cycle luteal timing of this intervention is ineffective. Commonly, one third of women undergoing surgical oophorectomy fall into this sub-group [10].

Specific surgical oophorectomy efficacy data according to hormonally -confirmed menstrual cycle phase

Two recently reported phase III clinical trials in adjuvant and metastatic populations address the hypothesis that surgical oophorectomy in patients who have low progesterone levels, but are in historical luteal phase (L_H) is relatively ineffective treatment [10, 11]. In the adjuvant trial, the primary analysis showed that L_H patients did not have better survival than patients in F_H (follicular phase by history) by strong trends (multivariable overall survival P=0.05) [10]. Exploratory analyses did not show any

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impact of delay of treatment. In preplanned analyses based on confirmed hormonal status, L_H patients with high progesterone levels (consistent with their historical phase) had better survival than L_H patients with low progesterone levels: the differences at 5 years were for disease free survival (DFS) 20%, multivariable P=0.03; and for overall survival (OS)15%, multivariable P=0.02. Among all randomized L_H patients: those with high progesterone had better survival than those with low progesterone (P=0.001). In the metastatic study, the primary analysis showed that luteal history and follicular history surgical oophorectomy patients had equivalent overall survival ($L_H=F_H$ for OS) [11]. In preplanned analyses, based on confirmed hormonal status L_H patients with high progesterone levels had better overall survival than L_H patients with low progesterone levels: 27 versus 17 months (multivariable P=0.14).

In summary, in two phase III trials, patients in luteal phase by history, but with blood levels of progesterone consistent with anovulatory status, (describable also as patients with prolonged follicular phases), consistently have lower benefit (if any) from surgical oophorectomies accomplished at these times. The corollary to this observation is that were such patients (as noted usually one third of patients) identified a priori, and not treated with this surgery at this time, those patients treated (in hormonally-confirmed follicular or luteal phases), would be expected to have better outcomes that the average outcomes that are seen from this treatment applied to all premenopausal women regardless of hormonal status and menstrual cycle phase. Thus, if in a high-risk group of women with operable breast cancer receiving SO (+T) (without paying any attention to their menstrual cycle history and blood levels of progesterone), 65% have no recurrence in 5 years; if patients have their SO in the first half of their menstrual cycles by history and with confirmation showing low

progesterone blood levels, 72% will have no recurrence in 5 years [3]. This increased level of benefit from appropriately timed SO, suggests that timed SO+T must be equivalent or better than LHRH + aromatase inhibitor, now touted as the most effective hormonal adjuvant treatment in premenopausal women [6].

Relevant menstrual cycle hormonal biology

What biological explanation is consistent with this observation? In low progesterone historical luteal phase patients (= anovulatory prolonged follicular phase patients), women have sustained high levels of estradiol from about day 7 through then to the time of their surgical oophorectomies-- from 7 to day 15 through perhaps day 22--- which exposure is not followed by "rescue" from high levels of progesterone because of the oophorectomies. In contrast, with oophorectomies in normal follicular phase, the exposure to estradiol is shorter in duration, and in normal luteal phase some progesterone "rescue' occurs before the oophorectomies precipitously drop the circulating levels of both estrogenic and progesterogenic hormones. In normal menstrual cycles without surgical oophorectomies the production of progesterone (at concentrations multiply higher than those of estradiol) in the luteal phase counteracts the stimulatory effects of estradiol in the follicular phase. The high, unopposed, and prolonged estradiol levels in low progesterone luteal phase patients stimulate growth of micro-metastases and are the last major signal that these lesions receive. This signal overwhelms the subsequent, presumably beneficial anti-growth effects of the oophorectomies themselves. As noted, the limited duration elevated estradiol exposure followed by oophorectomy in the follicular phase of a cycle appears to send a strong anti-growth signal, perhaps due to a "shock" effect with the sudden lowering of estradiol. In hormonal

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treatment of metastatic breast cancer, a flare of the disease is often seen about 7-10 days after starting the treatment, which has been interpreted as consequent to a stimulatory effect of the treatment. When such flares occur, they are usually followed by excellent tumor shrinkage responses. This flare model may be what is occurring with oophorectomy in the follicular phase of a menstrual cycle. In a normal luteal phase, as noted, increasing high concentration progesterone levels send their usual anti- growth signals, and oophorectomy may have relatively little sudden effects; the last signals, high progesterone-mediated, may be the most important and lead to the beneficial anti-micro-metastatic tumor cell effects.

These new data are showing extraordinarily high (and so unexpected) limited effects (in the sense of no benefit from oophorectomies) in designated anovulatory patients from limited time hormonal differences, while showing strong effects when this surgery is done in follicular or high progesterone luteal phases. Are there other external data which validate this conclusion? There are four observations consistent with this case. First, women who undergo surgical oophorectomy develop immediate and severe vasomotor symptoms suggesting that at least some tissues-cutaneous blood vessels- are hyper-sensitive to hormonal changes. Surgical physicians put estrogen patches on patients in the operating room because of these immediate effects. This is analogous to the posited "shock" effect of follicular phase oophorectomy.

Second, an observation about immediate, but salutary effects of major hormonal change on metastatic tumors or their surrounding stromal cells: men with metastatic prostate cancer have immediate favorable responses to orchiectomy. Again, this is analogous to the shock effect of follicular phase oophorectomy. Third, (and completely consistent with the suggestion

that the loss of progesterone "protection" with surgical oophorectomy with prolonged estradiol elevations in anovulatory women is harmful), are the results of a *Badwe et al.* study of short term parenteral peri-operative progesterone, which treatment was associated with better outcomes in axillary node positive patients [12]. This observation is then analogous to the explanation for the beneficial effect of high progesterone luteal phase oophorectomy, and consistent with the new data observation of absence of benefit with low progesterone luteal phase patients.

Four, and most significantly, the peaks of hazards for recurrence of breast cancer at 2-3 years post diagnosis and treatment have most strongly (and really only credibly) been related to peri-operative (and short-lived) changes in the interior milieu. In his model, *Baum* emphasized that minor peri-operative changes can have major effects (13). So, the idea that peri-operative conditions of limited duration might have immediate and major longer-term impacts is consistent with other important observations [14].

Some authors have suggested that useful data about the relative efficacies of SO LHRH will come from further analyses of the combined SOFT and TEXT trials data. In these trials however, 393/2033 patients had surgical oophorectomy or irradiation to the ovaries early or late as adjuvant treatment; this group is heterogeneous for other prognostic factors also [7]. These small numbers, the fact that this treatment group was not randomly determined, and multiple confounding variables, strongly support an opinion that any meaningful conclusions in this regard from these data are unlikely.

Conclusion

Low-progesterone historical luteal phase status is common among premenopausal women, particularly as women age into their 5th decade. Surgical

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oophorectomy in these women appears significantly ineffective as hormonal treatment for women with hormone sensitive breast cancers because of the different hormonal signaling that occurs in this situation, with prolonged estradiol stimulation of micro-metastases, without opposing progesterone rescue. The treatment benefits from surgical oophorectomy, which is a powerful therapy in hormone sensitive breast cancer, can be significantly greater, equivalent if not better than those from any hormonal treatment, if this sub-group of patients is identified and not given this treatment. 100,000 women a year worldwide could be saved were this affordable and practical approach to treatment universally adopted

Measurements of quality of care of LHRH +T versus Surgical oophorectomy + tamoxifen (SO+ T) (Institute of Medicine--IOM criteria 9)

Efficacy	Equivalent, but suggestion that SO+T can be more effective by selecting patients more likely to benefit, giving higher level of benefit equivalent to that positive from LHRH + exemestane (7). (Not possible with LHRH).
Safety	For bone mineral density, SO+T causes less loss/toxicity (16). SO demonstrated safe in studies in 1700 patients in several low- and middle-income countries, (10,11,16).
Cost- effectiveness or Net health benefit for cost	For patients, SO+T much more cost- effective or gives more net health benefit for much lower patient payment (3). (Surgery is a public health service in most countries.) SO+ T maximizes impact of medical resources for women with breast cancer. CEA: $350/year of life saved (16).
Patient-centeredness	SO+T more practical because of no need for multiple (for 5 years) monthly visits with additional direct and indirect patient costs. Offering SO option allows patient preferences, needs and values to guide clinical decision-making.
Timeliness	SO+T with surgery gives ovarian treatment promptly and completely with no delay.
Equity	SO+T provides consistent quality of care to all patients and is a much more socially just treatment.

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