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EDITORIAL

Adjuvant ovarian suppression for resected breast cancer: 2017 critical assessment

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Abstract Currently available data supporting adjuvant ovarian function suppression for resected breast cancer in premenopausal women in addition to standard chemotherapy and tamoxifen are not persuasive, even though an ASCO guideline supports them. Available information from the key trial, called "SOFT," has only 5-year follow-up in a 15-year disease. It employs breast cancer events as an endpoint, rather than distant metastases, or better still, death from any cause. The small advantages reported to date may disappear when aromatase inhibitors are given after the occurrence of menopause in the control population. Caution should be exercised in recommending ovarian suppression in all but the highest-risk situations.

Keywords Adjuvant ovarian suppression · Premenopausal breast cancer · Endpoints for adjuvant clinical trials

Introduction

During a review session at the end of the 2016 San Antonio Breast Cancer Symposium, an audience member raised the question of how to further treat a premenopausal woman who had just completed 5 years of ovarian function suppression (OFS) plus the aromatase inhibitor (AI) exemestane (EXE). The discussion made it clearly apparent that the bulk of expert opinion accepts as convincing the evidence favoring adjuvant OFS for higher-risk breast cancer in premenopausal women who retain ovarian function after perioperative chemotherapy. The author of this paper was the exception.

The goal of this paper is to clearly articulate the reasons for this skepticism. The principle that holds here is "If one is treating humans who feel well, then one has to be fairly certain that the treatment will either make a person live longer or live considerably better."

Statisticians see their task in evaluating clinical trials to decide whether one treatment is *different* from another, employing a selected endpoint. For clinicians, the establishment that one treatment is very likely better than another is just a starting point. Clinicians evaluate the extent and importance of the benefit, the toxicity of the intervention used to achieve the benefit, the strength of the evidence that the benefit is as large as is claimed, the relevance of the benefit to the patient, as well as how many patients must be subjected to the toxicities of the intervention for one patient to benefit.

OFS is clearly active in the treatment of both metastatic and resected localized breast cancer. The issue is not whether OFS is active, but whether OFS has sufficient activity when it is added to the multiple agents of modern adjuvant therapy of resected breast cancer to justify its use, despite its considerable subjective and objective toxicities. The published result of the key modern "positive" adjuvant OFS study (SOFT [1], with its associated study, TEXT [2]) has limitations in its data and analysis that make the extent of the benefit and confidence in the magnitude of the benefit uncertain. Further follow-up may fail to prove a significant benefit in reduction in distant metastases (which ultimately lead to death from breast cancer) and improvement in overall survival (OS).

The goal here is to briefly review data showing efficacy for OFS in breast cancer, the results of the relevant modern studies, and to explain why physicians should pause to

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think before unreservedly advocating adjuvant OFS based on them. This position opposes a recent ASCO guideline, which will also be summarized here.

Ovarian function suppression for metastatic disease

Beatson, in 1895, was the first to show that bilateral oophorectomy could relieve the symptoms of metastatic breast cancer in premenopausal women (his procedure was done together with oral dessicated thyroid!) [3].

Modern studies of OFS generally use drugs that work by suppressing pituitary gonadotropin production, rather than surgical bilateral oopherectomy or ovarian irradiation. OFS plus tamoxifen (TAM, an oral anti-estrogen) produces more remissions and longer overall survival (OS) in premenopausal women with metastatic breast cancer than OFS alone, and is the internationally accepted standard first therapy for metastatic hormone receptor-positive breast cancer in premenopausal women [4]. We have no studies proving that OFS plus TAM is superior to TAM alone in the treatment of metastatic disease, although we assume this to be the case because OFS is approximately as active as TAM in this setting [5], and OFS + TAM is more active than TAM alone. The considerable data favoring concurrent OFS and TAM for metastatic disease in premenopausal women argue that these interventions together should prove superior to either alone in the adjuvant setting, when the goal is preventing distant relapse and death from metastatic breast cancer.

Adjuvant ovarian suppression is clearly active when given alone

Adjuvant ovarian ablation(or resection) or OFS achieved via pituitary suppression is clearly effective at preventing relapse of resected breast cancer and death from breast cancer according to an individual patient meta-analysis [6]. The positive result is surprising because estrogen-receptor status was not tested in 63% of study subjects! The benefits of ovarian ablation or suppression were significant only if given alone, not with other therapy. This is consistent with the hypothesis that adding a drug to suppress ovarian function that has already been obliterated by chemotherapy will result in little benefit.

A later meta-analysis looking at adjuvant OFS using just LHRH (luteinizing hormone/releasing hormone) agonist/antagonist therapy (mostly given for only 2 years) had difficulty proving its benefit [7]. Only 338 patients were in the meta-analysis of LHRH agonist versus observation. The observed reductions of 28% in recurrence, 18% in death after recurrence, and 23% in death from any cause proved not statistically significant, perhaps because the numbers of events were small. Comparisons of outcomes of chemotherapy (CT) and TAM, given alone or together, with or without OFS, were similarly not statistically significant [7].

Comparative studies found OFS to be almost as active as CMF chemotherapy [6]. Older studies of OFS were complicated by lack of ER data on the primary tumor in substantial portions of the study subjects. More modern studies were complicated by the near universal use of adjuvant chemotherapy for higher-risk premenopausal women. Chemotherapy, especially if it is longer in duration and containing cyclophosphamide, often induces amenorrhea and ovarian endocrine failure. Especially among the older premenopausal women, it induces permanent menopause. Only the two most recent studies (SOFT and TEXT) dealt adequately with this issue.

ECOG 5188: OFS failed because ovarian failure was already present

The predecessor study for SOFT was ECOG 5188 (Intergroup 0101). The chairman of ECOG 5188, Dr. Nancy Davidson (now of Fred Hutchinson Cancer Center), reported improved disease-free survival (DFS—defined below) when 5 years of TAM was added to CAF chemotherapy(6 months of cyclophosphamide, adriamycin, and fluorouracil) plus 5 years of OFS, but not when OFS was added to chemotherapy alone in a generally "older" population of premenopausal breast cancer patients [8]. Menopausal status was assessed only before CT, and menopause likely occurred after CAF in most of the women over 40 at entry. OFS produced a nonsignificant 3% OS advantage in the entire population of patients, with a median follow-up of 9.6 years. For women younger than 40 years at entry, there were trends in DFS and OS in favor of adding OFS to CAF, and TAM to CAF + OFS, but they were far from statistically significant. The feeling was that OFS had been tested here in a population that had already largely been rendered postmenopausal by chemotherapy, and so could not help further.

SOFT and TEXT were undertaken because the issue was open around the year 2000 whether adding early ovarian suppression to the then standard program (5 years of adjuvant hormonal therapy with TAM, often preceded by 12–24 weeks of intensive CT with at least 3 drugs) would produce a longer or better life for younger women with resected breast cancer.

The design of SOFT and TEXT

Around the year 2000, a group of investigators, centered around the International Breast Cancer Study Group (IBCSG), set about designing studies to define the value of

OFS together with TAM, EXE, and CT in the treatment of premenopausal women with resected breast cancer. Three studies began accrual around 2003. One of these (PERCHE) focused on the value of adding chemotherapy to OFS plus either TAM or EXE (chosen at the discretion of the physician and patient). This study closed after three years, having accrued only 29 patients of a planned 1750.

The other two study designs were the result of a disagreement as regards the standard adjuvant hormonal therapy of premenopausal hormone receptor-positive resected breast cancer. For the largely European physicians who thought OFS to be the standard of care, TEXT assigned all patients to OFS for 5 years with at-random assignment to concurrent therapy with either TAM or EXE for five years. For the largely North American physicians, who thought the standard of adjuvant hormonal therapy was TAM, SOFT added a "control" arm of TAM alone to experimental arms of TAM + OFS and EXE + OFS.

As the studies began accruing patients, it became clear from the ATAC trial that adjuvant AI therapy is active for women without functioning ovaries, and is slightly more effective than TAM [31]. AIs act by profoundly suppressing the estrogen levels in blood and tissues of women who already have no ovarian endocrine function. Whether relapse of breast cancer in women undergoing a menopause after the diagnosis of breast cancer would be further prevented by this additional profound estrogen suppression was unknown in 2002. Only in 2013 did the data become available from MA.17 that introduction of profound estrogen suppression with an AI after 5 years of TAM was particularly effective in women who had been premenopausal at diagnosis, but later lost ovarian endocrine function [9]. The use of an AI in this setting produced a 74% reduction in disease-free survival (DFS) events compared to placebo—a huge benefit.

Both SOFT and TEXT allowed for the administration of initial chemotherapy according to the advice of the physician and the desire of the patient. Not surprisingly, chemotherapy was largely given to the higher-risk patients. Women with prior adjuvant or neo-adjuvant chemotherapy were eligible for entry into SOFT and TEXT only if they had biochemical evidence of intact endocrine ovarian function within eight months *after* completing any chemotherapy. This requirement addressed the major perceived problem with ECOG 5188: that OFS could not possibly help women whose ovaries had already ceased to function, presumably the case in the majority of women over 40 years old in 5188, all of whom had undergone CAF chemotherapy. This could have made 5188 a falsely negative study because of inadequate patient selection.

Endpoints for adjuvant breast cancer trials and eligibility considerations

Before going over the results of SOFT and TEXT, the utility and limitations of various endpoints employed and not employed in the analyses need to be reviewed for those not familiar with them. The argument to be made here is that OS is the definitive endpoint. The greater and more durable the improvement in OS, the more desirable the therapy. Since distant metastases are generally the cause of death in breast cancer, survival free of distant metastases is a reasonable, but somewhat flawed, surrogate endpoint when OS data are immature. Other surrogate endpoints are largely inappropriate for adjuvant treatments that produce major toxicity.

The proper and indisputable endpoint for trials of adjuvant therapy in lethal cancers is OS. Nearly all humans would like to delay death, provided that life is reasonably comfortable. The date of death is nearly always precisely known, and the event is irreversible. The problem for investigators in using OS as an endpoint in hormone receptor-positive breast cancer is that it takes 10–15 years for most of the cancer deaths to occur. This is longer than the duration of many of the grants funding studies, and of the patents that protect the interests of drug companies who fund studies. Further, many investigators will move on or die before the 15 year point. To these 15 years one must add at least 3 years of study development and approval, plus 5–10 years to accrue the study subjects.

DFS was chosen as the primary endpoint for SOFT and TEXT. As defined in the studies, it has the advantage of encompassing most everything bad that could happen to the patient, relating to cancer. It includes death from any cause, distant metastases from breast cancer, local recurrence in the breast, regional recurrences in nodes or skin, new primary breast cancers on either side, and new invasive cancers at any site. The latter is particularly relevant for breast cancer since TAM causes both carcinomas and sarcomas of the uterine fundus. DFS specifically excludes noninvasive cancers like ductal carcinoma in situ (DCIS), presumably because death is rarely associated with this condition. DFS seems a desirable endpoint because a lot of DFS events occur, and this makes statistical significance easier to achieve. On the other hand, many of the conditions included in the DFS endpoint are easily, and generally successfully, treated and often cured. Small new primary breast cancers, most endometrial cancers, and early colon cancers are in this category.

DFS might well be the optimal endpoint for a very gentle and nontoxic intervention which rarely impairs the quality of life and rarely shortens the duration of life. Such interventions include vitamin D supplements, daily aspirin

and NSAIDs, exercise, weight loss, dietary modifications, and the use of statin drugs.

For an intervention as toxic as five years of drug-induced menopause in a young woman, one would like to possess convincing information that the duration or quality of life is substantially improved. Since the results of treating early breast cancer have already become very good (witness the observed 77.1% 5-year DFS of even the higher-risk patients in TEXT who got chemotherapy and 5 years of TAM without OFS), most of the women subjected to adjuvant OFS will not benefit from it, because they will do well anyway. Given this large population of women who suffer substantial subjective toxicity from an early menopause but do not benefit from the therapy (since they do well anyway), it would be very difficult to show an overall quality of life benefit based on the delay of DFS events in the minority who did benefit from OFS. This means that, for the study result to be important to patients, it *must* show a substantial benefit in OS.

The way to get around the dilutional effect of better-risk patients (who would do well anyway) is to exclude most of them from the trial, leaving a very high-risk population. In such a population, preventing, or even just delaying, the terrible symptoms produced by metastatic breast cancer in a large proportion of the patients would likely improve overall quality of life, even though all the patients will suffer from the symptoms of an induced early menopause. One suspects that the designers of SOFT and TEXT chose not to restrict eligibility to such very high-risk patients because they thought there were too few of them to allow completion of study accrual in a reasonable time. It happened that outcomes of the control group in SOFT were considerably better than those of similar populations in earlier studies like ECOG 5188. Even if the designers of SOFT had tried to restrict eligibility to very high-risk women, it is not clear they would have found enough of them to run a study. Breast cancer outcomes in the late twentieth and early twenty-first centuries have markedly improved!

Distant recurrence-free survival (DRFS) is probably the best available early surrogate for OS. Distant metastases are almost always the mechanism by which breast cancer produces death. DRFS has the minor disadvantage of being dependent on the zeal and thoroughness of the search for distant metastases. Where funds are limited for sophisticated radiographic studies of mildly symptomatic patients, diagnosis of distant metastases will be delayed, although usually only by a few months before symptoms become severe. Further, in some parts of the world, biopsies of sites of suspected distant metastases are not available. This means that distant metastases may be coded when they do not actually exist. These patients will do very well indeed after distant metastases are diagnosed when they did not really exist.

In the 1990s in British Columbia, the median survival of women with metastatic hormone receptor-positive breast cancer was 2.2 years from the diagnosis of distant metastases for those with low proliferation in the primary tumor, and 1.6 years for those with high proliferation [10]. It may be much longer in the next decade with the availability of targeted therapies like mTOR (mammalian target of rapamycin) inhibitors and inhibitors of cyclins D4 and 6. These are already known to prolong time to progression of metastatic breast cancer by many months, and may well prove to prolong survival as well.

DRFS has recently been called into question as a surrogate endpoint for good prognosis breast cancer by the results of in MA.20. This trial of extended field adjuvant radiation after a mastectomy initially reported an impressive and significant benefit in DRFS in 2011 [11]. When the 10-year results were reported in 2015, however, the difference in OS was minimal and not significant [12]. The explanation for the failure of DRFS to predict OS remains unclear. Since distant metastases are the mechanism by which breast cancer generally produces death, if one must use an early surrogate marker, DRFS is the one to use until OS results become mature. As a surrogate, though, it remains flawed.

Two other surrogate endpoints were used in the analyses of SOFT and TEXT. The first is breast cancer-free interval (BCFI), which includes breast cancer metastases, local or regional recurrences, and new breast cancers, but excludes noninvasive breast cancers, new cancers of other organs, and deaths before any breast cancer recurrence. These early deaths are censored from the BCFI curves at the time of death. Because of this censoring of this most undesirable (to the patient) early event, BCFI is best considered a tool to explore what really happened in the study, rather than an endpoint that is relevant to the patient choosing therapy. As is the case for DFS, BCFI combines conditions that are easily and generally successfully treated with conditions that are uniformly lethal (distant metastases). SOFT and TEXT investigators used breast cancer-free rate (BCFR) at 5 years to report their results—these are summarized in Tables 3 and 4.

Distant recurrence-free interval (DRFI) looks only at metastases and censors any deaths that occur before distant metastases were documented. As is the case for BCFI, this censoring makes DRFI more suitable for data analysis and hypothesis generation than for advising patients on which treatment to choose for themselves. Distant recurrence-free rate (DRFR) at 5 years was used as a reporting tool in the SOFT paper—summarized in Tables 2 and 5.

TEXT results

TEXT and SOFT posed two separate questions. The first paper published in June, 2014 dealt with which oral hormonal manipulation, TAM or EXE, was the preferable partner for OFS [2]. This analysis included all the patients in TEXT and in two-thirds of the patients in SOFT.

Survival at 5 years was 96–97% in each arm, but analysis was appropriately considered premature since so few patients had died. DFS was about 4% better with EXE (91.1 vs. 87.3%, HR 0.72, 95% CI 0.60–0.85, $p < 0.001$), but only about 60% of the DFS improvement (affecting 2% of patients) was in survival without distant metastases (the augur of impending death from breast cancer). New cancers arising in non-breast sites accounted for 13.6% of DFS events.

Distant recurrence-free rate (DRFR) at 5 years was 92% for OFS + TAM and 93.8% for OFS plus EXE, (HR 0.78 95% CI 0.62–0.97, $p = 0.02$). Among the higher-risk chemotherapy treated patients, the absolute reduction in distant recurrence at 5 years from using EXE + OFS instead of TAM + OFS increased to 2.6% in TEXT and 3.4% in SOFT compared to 1.8% in the entire population. The latter included those without prior chemotherapy at lower risk. In applying this analysis, one needs to remember that, in DRFI analysis, deaths without documented recurrence before death were censored and not counted as events.

More women stopped all therapy early in the EXE arm (16 vs 11%). Both arms had a high percentage of depression (50%), insomnia (59%), fatigue (62%), hot flashes (92%), vaginal dryness (52% for EXE versus 47% for TAM), decreased libido (45 vs. 41%), and dyspareunia (31 vs. 26%), suggesting that early chemical menopause was difficult for these women.

SOFT results

Six months after the TEXT publication, the primary analysis for SOFT gave us the results for the control group relevant for most North American physicians, the group whose hormonal therapy was TAM alone [1]. The DFS advantage for TAM plus OFS compared to TAM alone (the primary study endpoint) just failed to achieve statistical significance. The DFS at 5 years from randomization was 84.7% for TAM alone and 86.6% for TAM plus OFS, an absolute difference of 1.9% that achieved significance (HR 0.78, CI 0.62–0.98, $p = 0.03$) only when the comparison was corrected for small imbalances in prognostic factors in the groups of approximately 1000 women each. Women with Her-2-positive cancers (about 12% of those entered) seemed to derive more benefit for OFS than the rest.

Distant metastases accounted for only 58.2% of DFS events, and 12% of DFS events were new non-breast primary cancers. There is no reason to assume that OFS would decrease the incidence of new non-breast primary cancers, so including them in the endpoint dilutes any observed benefit from OFS.

The results for better-risk patients who had been selected *not* to receive chemotherapy were remarkably good, whether or not they were subjected to OFS. These women were 92% over 40 years old at entry, 91% had negative axillary nodes, 85% had primary tumors 2 cm or less in diameter, 92% had tumors that were grade 1–2, and 96% had tumors that were her-2 negative. Of the 476 women without prior chemotherapy at entry randomly assigned to the TAM control group, only 6 had distant relapses and only 2 had died, with a median follow-up of 67 months in SOFT. One-third of DFS events for these women were not related to breast cancer. Freedom from breast cancer was >95% at 5 years. When these good-risk women were included, the primary analysis did *not* show a significant benefit in disease-free survival (DFS) for the addition of OFS to TAM. The good-risk patients diluted any DFS benefit among those with higher risk.

It is very difficult to conceive of a study of finite size that could establish the efficacy of a treatment to improve on the results observed so far in these good-risk women. These patients, chosen on clinical grounds (rather than the gene expression profiling that is now commonplace), do very well without OFS or CT, and should get neither, according to expert opinion justly enshrined in the ASCO guidelines. Unfortunately, we do not have exact criteria for selecting these women *not* to have CT: none were specified. We have only their known clinical characteristics.

With a negative result for the primary endpoint, the SOFT investigators proceeded to a planned subgroup analysis of those higher-risk women who had been selected to receive initial chemotherapy and were entered after they proved to have preserved endocrine ovarian function within eight months of finishing the chemotherapy. This selection criterion had never before been used for a clinical breast cancer study. They were analyzed separately because they had special entry criteria to enter the protocol (relating to demonstration of preserved ovarian function), and their treatment assignment was separately stratified. These women at entry were 49% less than 40 years old, 57% node positive, 47% had primary tumors greater than 2 cm, 18% had her-2-positive primary cancers, and 35% had grade 3 cancers.

This group proved to have a moderate risk of DFS events: 5-year DFS was 77% with CT + TAM and 81% with CT + TAM + OFS. The 5-year OS was 90.9% for CT + TAM and 94.5% for CT + TAM + OFS (Table 1). This represents a hazard ratio (HR) of 0.64 with 95%

confidence interval (CI) of 0.42–0.96, and so was statistically significant despite its obvious prematurity.

Small numbers and short follow-up may also be the factors to blame for the unexpected slight survival disadvantage for OFS + EXE compared with OFS + TAM noted in Table 1. Of concern, though, is the similarity to the adverse effect on OS of using the AI anastrozole instead of TAM with OFS in ABCSG 12 [13]. A recent meta-analysis of SOFT, TEXT, and ABCSG 12 reports that OFS plus TAM has 65 more DFS events than OFS plus an AI, but the latter was associated with 30 more deaths! [28]. This disconnect between distant relapse and mortality makes the authors urge caution in deploying adjuvant OFS plus an AI among premenopausal women with early breast cancer. It may be that the early and very profound estrogen suppression produced by OFS plus aromatase inhibition produces even more "off-target" lethal effects than those already documented for premenopausal surgical oophorectomy alone for women without breast cancer [29].

When comparing DRFI for CT + TAM versus CT + TAM + OFS (Table 2), the HR is 0.87; the difference in events is only 8, and the confidence interval overlaps unity. For CT + TAM versus CT + EXE + OFS, the difference in events is 23 (among about 543 women per arm), the HR is 0.72, and the 95% confidence interval reaches 0.98. The prevention or delay of eventually fatal distant metastases is the reason why we administer adjuvant systemic therapy to women with resected breast cancer. Because the difference in DRFI is borderline and the follow-up short, SOFT provides just suggestive evidence that CT + OFS + EXE shows significantly improved results over that achieved with CT + TAM without OFS. Also, there is a distressing disconnect between early OS and DRFI.

The analysis of BCFI attracted the most interest when Dr. Prudence Francis presented SOFT at the 2014 the San Antonio Breast Cancer Symposium. The results for all patients are given in Table 3, but the results for women <35 years old at entry generated the most discussion (Table 4). The 350 women in this analysis constitute only 11% of the total SOFT population: 94% of them were entered after prior CT. The difference in BCFI events was 15 between TAM and EXE + OFS. The 95% confidence intervals for 5-year BCFR in the best and worst arms both just overlap (Table 4).

Table 1 OS in SOFT patients entered after chemotherapy

Arm	Number	Events	5-year OS, %	HR	95% CI
TAM	542	57	90.9		
TAM + OFS	542	39	94.5	0.64	0.42–0.96
EXE + OFS	544	50	92.3	0.87	0.59–1.27

HR hazard ratio, OS overall survival

In mid-2017, we finally saw the detailed analysis of events for the <35 population, now appropriately restricted to those who received prior chemotherapy and whose primary cancers were her-2 negative [32]. This analysis of DRFR at 5 years is summarized in Table 5. From these data in this population, it is likely that OFS adds very little or nothing to TAM in preventing distant recurrences at 5 years, and that substituting EXE for TAM with OFS contributes little (SOFT result) or nothing (TEXT result) to reducing the distant recurrences at 5 years. These results are very disappointing.

The progressive benefits of adding OFS to TAM and then substituting EXE for TAM in addition to OFS (shown in Table 4) seem lost in this newly available analysis of distant metastatic interval in women <35 at entry. Part of the reason may be that in removing patients with her-2-positive cancers from the analysis, the investigators also removed those who benefitted most from OFS in prevention of distant metastases (those with her-2-positive primaries had the largest DFS benefit from OFS in the primary analysis of SOFT). Also , by reducing the population at risk to 240 (a consequence of restricting the analysis to patients with her-2-negative primaries randomized after chemotherapy), the number of events becomes quite small and liable to random variation—especially in a dataset where half the patients have not passed the 67-month mark. If all the patients had been followed out to 5 years, the maximum number of distant events separating the best and worst arms of SOFT in this <35 population would be 8. This maximum difference of 8 distant events at 5 years fails to justify the enthusiasm with which these data have been quoted as demonstrating a progressive decrease in significant breast cancer events from the addition of OFS and the use of EXE instead of TAM without OFS. For valid statistical reasons, Dr. Meredith Regan (the lead statistician for SOFT and TEXT) did not choose to formally compare the outcomes in the <35 patients for DRFI and BCFI.

Toxicity of OFS

Table 6 gives selected relevant toxicities reported for TAM alone vs TAM + OFS—the only direct comparison we have in the two trials that isolates the toxic effects of OFS.

These were further explored using instruments of patient reported outcomes in 2016 [14]. This analysis showed that women in SOFT who had prior CT already had worse baseline scores for the endocrine and gynecologic toxicities of OFS. This should be expected, since CT will almost universally produce a period of amenorrhea and OFS during the therapy. The return of ovarian function is neither immediate nor immediately complete. The quality of life

Table 2 Five-year DRFR in SOFT patients entered after chemotherapy

Arm	Number	Events	5-year DRFR (%)	HR	95% CI
TAM	542	90	84		
TAM + OFS	542	82	85	0.87	0.64–1.17
EXE + OFS	544	67	88	0.72	0.52–0.98

Median follow-up, 67 months

EXE exemestane, *HR* hazard ratio, *OFS* ovarian function suppression, *TAM* tamoxifen

Table 3 Five-year BCFR in SOFT patients entered after chemotherapy

Arm	Number	Events	5-year BCFR (%)	HR	HR 95% CI
TAM	542	116	78		
TAM + OFS	542	97	82.5	0.78	0.60–1.02
EXE + OFS	544	80	85.7	0.65	0.49–0.87

BCFR breast cancer-free rate, *HR* hazard ratio, *OFS* ovarian function suppression, *TAM* tamoxifen

Table 4 5-year BCFR in SOFT patients <35 years old

Arm	Number	Events	5-year BCFR (%)	95% CI
TAM	112	34	68	57–76
TAM + OFS	121	27	79	70–86
EXE + OFS	117	19	83	75–89

BCFR events include distant metastases, ipsilateral in-breast recurrences and new invasive cancers, contralateral invasive new primary breast cancer, and regional recurrences

94% of these women had chemotherapy before entry

BCFR breast cancer-free rate, *EXE* exemestane, *OFS* ovarian function suppression, *TAM* tamoxifen

Table 5 5-year DRFR in patients <35 years OLD with prior chemotherapy and her-2-negative cancers

Study	ARM	Number	5-year DRFR (%)	95% CI
SOFT	TAM	79	74.6	63–83
	TAM + OFS	77	77.3	66–86
	EXE + OFS	84	84.4	74–91
TEXT	TAM + OFS	66	80.9	68–89
	EXE + OFS	79	81	68–89

(QOL) surveys in patients with prior CT showed no difference between TAM and TAM + OFS in vaginal discharge, vaginal itching/irritation, bone or joint pain, coping, and treatment burden. The addition of OFS was associated with a modest decline in sexual interest compared to TAM alone at 6 and 24 months, but was about equal to the TAM group at 60 months, perhaps because many of the TAM group women by that time had failing ovarian function (data to support this speculation were not reported).

Hot flashes were much more pronounced in the CT + TAM + OFS group at six and 24 months, but by 60 months both groups were about the same in their hot flash scores. The report did not break out QOL for women <35 years of age, where one would expect more pronounced endocrine and gynecologic toxicity. However, 94% of these had received chemotherapy before entry, and so made up about 20% of the "prior chemotherapy" cohort. Whether these women had greater or lesser compliance with QOL form submission and protocol therapy is not started in the paper.

The analysis of patient reported outcomes makes the stakes much smaller in the decision regarding whether to suppress ovarian function for 5 years after adjuvant chemotherapy, at least in terms of short-term subjective toxicity. Most of the problems one would have attributed to OFS have already been caused by chemotherapy. The addition of OFS exacerbates only the hot flashes and loss of sexual interest, and these are worse for less than 5 years.

Perhaps more important are the deleterious effects of early loss of ovarian function(without aromatase inhibition) on cardiac disease and cardiac mortality (increased 1.93 fold in a Mayo Clinic analysis [29]), impaired cognition, anxiety and early dementia, mood, sexual function and early osteoporosis [29]. Chemotherapy without intentional OFS leads to early menopause and impaired ovarian endocrine function. The exact extent to which OFS for 5 years adds to these problems in the longer term is still unknown. The severity of the life-long "off target" toxicities argues that we should require a benefit in OS that is both large and durable to justify the toxicities and risks both of OFS alone and especially with an AI.

The ASCO guideline

The American Society of Clinical Oncology (ASCO) convened a clinical guidelines panel in 2015 to recommend appropriate adjuvant endocrine therapy for premenopausal women with hormone receptor-positive cancers in light of

Table 6 Selected toxic effects of TAM and TAM + OFS from SOFT

Effect	TAM-all grades (severe) (%)	TAM + OFS-all grades (severe) (%)
Hot flashes	80 (8)	93 (13)
Depression	47 (4)	52 (13)
Sweating	48	62
Insomnia	46 (3)	57 (5)
Fatigue	60 (3)	63 (4)
Osteopenia	12	18
Vaginal dryness	42	50
Fractures	4.9 (1)	5.4 (1)
Dyspareunia	24 (1.4)	26 (2)
Urinary incontinence	16 (1)	18 (1)

the results of SOFT and TEXT, and 2 other recent studies. The final guideline was approved in November, 2015, and published online February 16, 2016 [15].

The guideline committee considered two other studies aside from SOFT and TEXT as new and possibly relevant. ABCSG 12 randomized low-risk premenopausal women to 3 years of OFS with either TAM or the AI anastrozole, with or without zoledronate [13]. All of the patients in the trial had OFS, so the trial cannot address the value of OFS. An American Intergroup study of TAM with or without OFS was closed early with only 345 patients and small observed differences in DFS and OS, failing to meet statistical significance [16]. It was severely underpowered to draw any conclusions, and so will not be discussed further here.

The ASCO guideline is clearly and thoughtfully written, and includes a detailed summary of the design, conduct, and analysis of the appropriate trials. The gist of the recommendation is that premenopausal women with higher risk of recurrence, metastasis, and death from breast cancer should get OFS in addition to either TAM or an AI. Higher risk is generally defined as bigger, node positive, higher histologic grade, or sufficiently ominous (for these reasons as well as young age) to warrant a recommendation in favor of CT in addition to hormonal therapy.

The guideline recognizes that the decision to give chemotherapy has been based on parameters that have changed over time, and that this decision is often particular to the preferences of the patient and the opinions of the physician. The guideline suggests that if the risk of recurrence appears high enough so that many physicians would give CT, adjuvant OFS should be prescribed. The justification for the recommendation is that "ovarian suppression is likely to achieve measurable gains in disease-free survival that would justify therapy."

The guideline panel overall recommended that OFS be applied either with TAM or an AI, though it favors an AI with OFS "for higher risk and younger women." The panel emphasized the difficulties encountered in assuring the presence of sufficient ovarian suppression to allow AI's to function and prevent recurrence and metastasis. The guideline correctly notes that in SOFT/TEXT the AI exemestane, when given with OFS, improved not only DFS but breast cancer-free survival. Apparently, the improvement in DFS but not OS was sufficient to warrant a favorable recommendation for OFS but not for the addition of EXE to OFS. This distinction may have been drawn because of the results of ABCSG 12, in which anastrozole produced inferior OS compared to tamoxifen when given with 3 years of OFS, alone or with zoledronate [13]. The other possible rationale was the panel's "inclination to offer AI therapy at some point to women treated with ovarian suppression." This presumably refers to AI use after menopause occurring while or after the patient received adjuvant TAM [9].

The guideline repeatedly and appropriately emphasizes the need for the physician to weigh with the patient both the advantages and the toxicities of OFS, and also the enhanced efficacy and worsened toxicities when OFS is initially combined with an AI rather than TAM. One cannot fail to support this position.

To the extent that the guideline, as written, will force insurance companies and prescription plans to pay for injections that suppress pituitary and ovarian function when patient and physician agree that these are needed, the guideline is a wonderful document. One is concerned that the strength of the recommendation in favor of adjuvant ovarian suppression, coupled with the high stature of both ASCO and the members of the guideline panel, will lead busy physicians who remember only guideline conclusions to apply it too broadly. Most or all young women with breast cancer should *not* be told that they must have OFS because everyone agrees upon it. Even among higher-risk patients, most of the women who will be offered OFS will do very well without it, based on the currently available data.

The guideline appropriately emphasizes that women with really low-risk, small, node-negative, low and intermediate grade tumors in TEXT who got only TAM did very well without OFS and without chemotherapy. The guideline also acknowledges many, but not all, of the limitations to the data to be emphasized here. These are summarized in Table 7 and discussed below.

Conclusions are based on suboptimal endpoints

The correct endpoint for a trial of adjuvant therapy given to women without symptoms, some of whom are already cured, is OS. DRFS (distant recurrence-free survival) is a somewhat flawed surrogate for OS, but at least focuses on

Table 7 Problems with SOFT/TEXT analysis

Short follow-up—5 years in 15 year disease
Wrong endpoints—breast cancer events versus distant metastases or overall survival
Late switch to AI after menopause on TAM may negate an early advantage for OFS + AI
Effective endocrine adjuvant therapy after 5 years of OFS + AI has not been established, and may not exist
Modern criteria for assessing risk of metastases and benefit from chemotherapy differ from those used when TEXT/SOFT accrued and may affect benefit from OFS in complex ways
In a meta-analysis, OFS + AI produced 65 fewer DFS events but 30 more deaths than OFS + TAM—early profound estrogen suppression in young women may do more harm than good

recurrences that eventually all prove lethal. SOFT and TEXT, as published, have too few OS and DRFS events to allow a meaningful analysis and secure conclusions. The investigators and their statisticians assure us that follow-up will continue and that eventually will get more and longer information on DRFS and OS—data we need to determine whether OFS is sufficiently effective to be a part of modern adjuvant breast cancer therapy.

The DRFI data released in mid-2017 for those with her-2-negative cancers treated with initial chemotherapy and <35 years old at entry should blunt the initial enthusiasm for OFS in very young woman with higher-risk breast cancer [32]. The numbers of subjects and events are too small and the follow-up too short to exclude that a meaningful benefit will later emerge. However, the trivial absolute benefit from adding OFS to TAM and the small and inconsistent benefit of switching to EXE from TAM combined with OFS offer scant support to enthusiastic and widespread employment of OFS in this population to prevent distant recurrences.

The surrogate endpoints used in the first two SOFT and TEXT publications [1, 2] (DFS and BCFI) include too many events that are generally well treated and rarely fatal (local recurrences, new invasive cancers in breast and other primary sites). Surrogate endpoints that censor deaths without prior breast cancer events are very good for generating hypotheses and honing analyses, but are not appropriate for advising patients, because the humans as a rule prefer to defer death, regardless of its cause. Attribution of cause of death is uncertain, while death itself remains the best endpoint for trials treating lethal diseases in humans.

Follow-up for SOFT and TEXT much too short

SOFT and TEXT were published with median follow-up of about 5.5 years and the follow-up publications are still using this analysis [32, 33]. Hormone receptor-positive breast cancer has a significant rate of systemic relapse out to 15 years. In British Columbia in the 1990s, median survival of hormone receptor-positive breast cancer after systemic relapse was 2.2 years for women whose primary cancers had low proliferation and 1.6 years for those with more proliferative primaries [11]. Therefore, we need to follow relapsing patients for at least that long to record the times of their deaths. This means that OS after 5 years reflects mostly distant metastases that occur only in the first 3 years or so.

Survival after distant relapse may be longer now than 20 years ago because we have more sensitive tests to detect metastases earlier, and because we have more effective endocrine therapies that produce longer remissions and may produce longer survival. The BCFI analysis of SOFT suggests that some relapse events are delayed or prevented by OFS, but does not exclude the possibility that the control group will catch up to those initially exposed to OFS as they later lose ovarian function and get further endocrine therapy.

The analysis ignored the efficacy of endocrine therapy after 5 years of Tam

By publishing results after a median follow-up of just over 5 years, any possible disproportionate benefit of later therapy is missed because it would occur after the analysis. There are strong reasons to suspect that late hormonal therapy will affect DFS and OS.

When SOFT and TEXT were designed, 5 years of endocrine therapy were a newly established standard. Only in 2003(the year SOFT and TEXT started accrual) were the results of MA.17 published showing that an AI(letrozole) after 5 years of TAM reduced DFS events in postmenopausal women with resected breast cancer [17]. Even then, there was a concern that patients premenopausal at diagnosis who lost ovarian function before the 5-year point would not benefit from further decreases in estrogen levels induced by blockade of aromatase.

Later analysis of the same MA.17 dataset dramatically showed the opposite. The benefit is particularly high for women who were premenopausal at diagnosis and later experienced a menopause before the completing 5 years of adjuvant TAM [9]. For this group, the HR for DFS was

0.26 in favor of the AI letrozole—a huge benefit. Based on these results, the standard treatment before SOFT and TEXT were presented was TAM for 5 years followed by an AI for 5 years for those women premenopausal at diagnosis with a later menopause (often chemotherapy-hastened). The optimal duration of AI therapy remains uncertain even in 2017, but most oncologists follow the 5-year course chosen for the MA.17 protocol [35].

Treatment after the first 5 years is not specified in SOFT or TEXT, and probably has changed a lot from December, 2008, to January, 2016, when the first patient and last patients to enter SOFT reached the 5-year point. Some patients probably got an AI, especially the older ones (who experienced menopause on taking TAM without OFS). Those that tolerated EXE well on during the study may have continued EXE. Some probably got extended TAM after ATLAS was presented and published [18]. Some probably continued OFS, with or without an AI. Some may have switched from EXE to TAM, even though no data are available to show that TAM prevents distant metastases or death in this setting.

The argument has been made that OFS allows the use of effective AI therapy, and that this is more effective than chemotherapy followed by TAM alone. The number of additional distant recurrences prevented at five years by adding OFS and substituting EXE for TAM is just 23 distant recurrences/544 entered per arm in SOFT (Table 2). This slim difference could disappear with further follow-up and further effective endocrine therapy in the TAM groups. The latter is only known to be effective in women initially treated with TAM, not an AI [35]. Recent studies have identified both a switch to an AI and another five years of TAM as active after the first 5 years of TAM. No therapy has yet been shown to have substantial activity after 5 years of an AI. Mechanisms of AI resistance frequently involve estrogen receptor activating mutations that also confer TAM resistance. This implies that neither may prove effective against many of the cancers already exposed to an AI for 5 years. Fulvestrant, an irreversible binder of the estrogen receptor that lead to receptor degradation widely used to treat metastatic breast cancer, does lead to apoptosis in breast cancer cells bearing activating estrogen receptor mutations. Alas, we have no data in humans that fulvestrant prevents breast cancer relapse or metastases for women with resected breast cancer. These studies have just not been done!

The SOFT investigators assure us that information is being collected on the continued treatment being offered to women in SOFT and TEXT, and we will be able to use this to interpret treatment effects on distant metastases and OS over another 10 years of follow-up. The heterogeneity of treatment after 5 years will likely make analysis of the benefits of initial OFS difficult.

Little benefit from hormonal therapy after AI For 5 years

The apparently preferred arm of SOFT and TEXT after chemotherapy was OFS plus EXE, based on the rate of DFS events. This treatment suffers from a paucity of data showing that further endocrine therapy is effective after 5 years of an AI. In contrast, we know that more TAM improves survival after 5 years of TAM [18, 19], and an AI improves DFS after 5 years of TAM [9, 17]. By the end of 2016, one study had been published [20] and 3 more had been presented at the 2016 San Antonio Breast Cancer symposium showing little or no benefit for extending AI therapy beyond 5 years except for continued suppression of new contralateral breast cancers [21–23]. Three of the studies show a very small reduction in distant metastases, but none shows even a hint of improved OS. A fifth study of more than 2000 women with 5 years of prior AI therapy evaluated an attempt to kill surviving breast cancer deposits by inserting an annual 3-month drug holiday in 5 years of further AI therapy. This study(called SOLE) failed to show a DFS benefit compared to continuous AI for an additional 5 years [32]. We therefore have no evidence that continued endocrine therapy beyond 5 years of EXE and OFS will do the patient much good [35].

On the other hand, women who got initial TAM can continue TAM with benefit as shown in Atlas and ATTOM [18, 19], and then switch to an AI after their menopause, with a marked reduction in breast cancer events [9]. One notes that OFS + TAM prevents relatively few early distant recurrences compared to TAM alone among the chemotherapy–treated patients in SOFT: 8 events among 542 patients in each arm (Table 2). This is true even for those <35 whose tumors are her-2-negative (Table 5) [33]. SOFT data so far do not convince us that we have to subject young women to an early menopause to improve ultimate outcomes. We need a significant and substantial OS advantage at 10 or 15 years to do that.

Minor issues with applying SOFT and TEXT

If further follow-up and analysis were to show that early application of OFS prolongs OS even though the control group receives further effective endocrine therapy, physicians would still have difficulties applying early OFS based on SOFT and TEXT.

First, the criteria by which physicians assigned patients to chemotherapy or none in 2003–2008 are not clearly defined, so we cannot reproduce them. It was clearly a combination of primary size, number of positive nodes, histologic grade (with or without separate determination of proliferation), extent of hormone receptor positivity, and age.

In 2017, the determination that CT is unnecessary because the prognosis is so good without CT is assisted by gene expression profiling using tests like ONCOTYPE-DX and Mammaprint. Data on exactly how good are the outcomes for women with higher clinical risk profiles but favorable gene expression profiles on hormones alone are still awaited for the ONCOTYPE-DX (from studies called TAILOR-RX for node-negative women and RX-PONDER for those with 1–3 involved nodes). The MINDACT trial has reported a 5-year rate of death or distant metastases of 5.3% for women with high clinical risk but low genomic risk by the Mammaprint assay [24]. This DDFS is clearly worse than that observed in the "no chemotherapy" cohort of SOFT, but was improved by only 1.5% by adding chemotherapy. Almost half the MINDACT patients had axillary metastases, while only 9% of the SOFT patients chosen to receive no chemotherapy had these. Whether the result is "good enough" not to add OFS or CT remains open to discussion. The MINDACT investigators focused their trial on sparing patients unnecessary CT, and did not address OFS.

There were only about 258 women with hormone receptor-positive tumors, less than 50 years of age with high clinical and low genetic risk, who entered into the no-chemotherapy arm of MINDACT, so the 95% confidence interval for 5 year DRFS (if we had this outcome for the subgroup for which consideration of OFS is appropriate) must be fairly broad. Ten-year data on DRFS from MINDACT may prove re-assuring in that low genetic risk mitigates high clinical risk. For 2017, physicians need to remember that we spare some women chemotherapy now that we would have treated in 2003, and that we may be tolerating higher risks of breast cancer death as a result. How this impacts on efficacy of OFS is uncertain.

Second, gene expression profiling has affected the decision to recommend CT for those with low clinical risk. Chemotherapy is clearly beneficial only for the cohort with recurrence score (RS) >31 in the ONCOTYPE-DX assay [25]. Women with low-risk cancers on clinical grounds now are offered chemotherapy for a high RS in anticipation of a 74% reduction in 10-year distant recurrence from 6 months of CMF chemotherapy. Offering this group OFS after chemotherapy is problematic because their remaining risk may be quite small (making the absolute benefit from the addition of OFS even smaller) and because the high RS also indicates resistance of the cancer to TAM that may also indicate resistance to another hormonal intervention like OFS. The ONCOTYPE-DX was consciously developed to indicate prognosis of TAM-treated women. The Mammaprint was developed in mixed population of women less than 55 years old given no adjuvant therapy, but presumably favorable gene expression includes markers both of endocrine dependence and responsiveness. No data are available to indicate that women at high risk only because of gene expression data will benefit from OFS added to CT + TAM or from OFS + EXE substituted for TAM and added to CT.

Third, the CT we use has changed to some extent, so that regimens used commonly in 2017 may be somewhat less toxic to the ovaries than those used in 2003. This affects the ovarian reserve of the population offered OFS after chemotherapy. It is conceivable that the current population receiving less or no cyclophosphamide may be larger, because more women have recurrence of their menses, but closer to menopause, since their ovaries may fail sooner. The sooner these ovaries experience endocrine failure, the less the benefit of OFS, since, once the ovaries have failed, OFS is unnecessary.

Fourth, the population <35 years old in SOFT and TEXT is inadequately characterized to use as a basis for current decision-making based on BCFI. Women with incident breast cancer aged less than 35 now have routine screening for deleterious mutations in ≥25 genes at the time breast cancer is diagnosed. The BRCA-1 and -2 screening tests available in 2003 were much less commonly deployed and more expensive than the currently used tests. The reductions in invasive breast cancer events (BCFIs) seen in SOFT in this subpopulation may in part relate to reductions in new breast primaries from the established effects of estrogen suppression on breast cancer incidences in BRCA-1 and especially BRCA-2 carriers. These women now have oophorectomies at the earliest suitable moment to reduce risk of lethal ovarian cancer, so the question of adjuvant OFS for them will rarely arise. Inclusion of an uncertain number of women with hereditary breast cancer probably increased the number of non-metastatic breast cancer events (largely new contralateral breast cancers) in those <35 in SOFT. The DRFI data released in 2017 show less benefit than BCFI data released earlier [33]. Perhaps the exclusion of in-breast events in mutation carriers is one of the causes. As the analysis matures and is restricted to metastatic events and OS, this issue will become less important.

Fifth, ovarian suppression of estrogen production is not always achieved by the monthly administration of an LHRH agonist antagonist, especially in obese women [26, 27]. An endocrine substudy of SOFT involving serial hormone determinations in 116 patients who were medication compliant showed that 17% of women assigned to EXE+OFS had estradiol levels above postmenopausal levels one year after start of therapy [34]. Further, 34% had at least one estradiol level measured in the first year above this threshold.

If one deems OFS necessary, then levels of estradiol, follicle stimulating hormone, and luteinizing hormone should be continuously monitored to ensure that estradiol is

indeed suppressed. The latter is critical to achieving any benefit from aromatase inhibitor therapy. An alternative is surgical bilateral oophorectomy.

Sixth, the benefits of medical OFS may be underestimated in the SOFT results for 2 reasons:

1. Some of the patients may be already postmenopausal. In the endocrine substudy of SOFT, 35% of the 116-patient subsample had centrally determined postmenopausal estradiol levels at entry [34]. There can be little benefit expected from medication inhibiting the function of ovaries that have already stopped functioning.
2. Poor compliance dilutes the ability of studies to detect differences that actually exist. In SOFT, 19% of all the enrolled patients stopped all their hormonal therapy. Nonadherence to medical OFS with triptoelin affected 10% of patients at year 1 and 23% at year 4 [34].

Seventh, the reversibility of OFS with return of cyclic ovarian function after 5 years of ovarian suppression has not been clearly demonstrated. One suspects that a certain proportion of women will have very limited or no recovery, and that this proportion will vary with the intensity of the antecedent chemotherapy (dependent especially on the cumulative dose of cyclophosphamide) and with the increasing age of the patient. After 2 years of goserelin OFS in IBCSG study VIII, 50% of women 40 years old and greater did not immediately recover menses, although 90% of those $\leq$39 did so [30]. Adding CMF chemotherapy to goserelin further impaired recovery of menses in both age groups in IBCSG VIII.

Even though all the patients in SOFT assigned to OFS +TAM after chemotherapy had recovered menses, one would expect a significant incidence of early menopause in these women both from the chemotherapy and the years of pituitary and ovarian suppression. The patients need to be informed of this effect, which many would find undesirable.

Summary

Adjuvant systemic therapy of resected breast cancer should be given to make patients live longer or live better. The majority of higher-risk, hormone receptor-positive patients receiving modern treatment programs without OFS live long lives without distant relapse. If exposed to OFS, many of these women will suffer from hot flashes and loss of sexual interest for up to 5 years without personal benefit, and some may experience early death from noncancer causes. The early subjective toxicity means that it is futile to hope that OFS will be associated with an improvement in quality of life in the entire population of patients. Hence, adjuvant OFS can only be recommended if it prolongs OS to a substantial extent. Data from prospective randomized trials to demonstrate this are so far lacking.

Further follow-up of SOFT and TEXT may provide these data. The utility of adjuvant OFS in addition to modern therapy remains uncertain. The surrogate endpoints used to date include too many easily treatable, nonlethal events to justify the severe toxicities of 5 years of OFS. Perhaps physicians should discuss adjuvant OFS only with those breast cancer patients at extraordinarily high risk of distant relapse with preserved ovarian function after chemotherapy, but not any others. Even for these women, we lack definitive evidence of benefit in OS. An early detriment in OS for OFS+AI argues against the adoption of OFS+AI until and unless more data show that this observation is spurious.

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