Surgical ovarian suppression for adjuvant treatment in hormone receptor positive breast cancer in premenopausal patients

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HIGHLIGHTS

- Ovarian ablation for adjuvant breast cancer treatment was offered to women with high-risk features
- A total of 45% of patients undergoing ovarian ablation had therapeutic bilateral salpingo-oophorectomy
- Complication (5.4%) and readmission (1.8%) rates after bilateral salpingo-oophorectomy were low

ABSTRACT

Objective Ovarian suppression is recommended to complement endocrine therapy in premenopausal women with breast cancer and high-risk features. It can be achieved by either medical ovarian suppression or therapeutic bilateral salpingo-oophorectomy. Our objective was to evaluate characteristics of patients with stage I–III hormone receptor positive primary breast cancer who underwent bilateral salpingo-oophorectomy at our institution.

Materials and methods Premenopausal women with stage I–III hormone receptor positive primary breast cancer diagnosed between January 2010 and December 2014 were identified from a database. Patients with confirmed *BRCA1/2* mutations were excluded. Distribution of characteristics between treatment groups was assessed using χ^2 test and univariate logistic regression. A multivariate model was based on factors significant on univariate analysis.

Results Of 2740 women identified, 2018 (74%) received endocrine treatment without ovarian ablation, 516 (19%) received endocrine treatment plus ovarian ablation, and 206 (7.5%) did not receive endocrine treatment. Among patients undergoing ovarian ablation 282/516 (55%) received medical ovarian suppression, while 234 (45%) underwent bilateral salpingo-oophorectomy. By univariate logistic analyses, predictors for ovarian ablation were younger age (OR 0.97), histology (other vs ductal: OR 0.23), lymph node involvement (OR 1.89), higher International Federation of Gynecology and Obstetrics (FIGO) stage (stage II vs I: OR 1.48; stage III vs I: OR 2.86), higher grade (grade 3 vs 1: OR 3.41; grade 2 vs 1: OR 2.99), chemotherapy (OR 1.52), and more recent year of diagnosis (2014 vs 2010; OR 1.713). Only year of diagnosis, stage, and human epidermal growth factor receptor 2 (HER-2) treatment remained significant in the multivariate model. Within the cohort undergoing ovarian ablation, older age (OR 1.05) was associated with therapeutic bilateral salpingo-oophorectomy. Of 234 undergoing bilateral salpingo-oophorectomy, 12 (5%) mild to moderate adverse surgical events were recorded.

Conclusions Bilateral salpingo-oophorectomy is used frequently as an endocrine ablation strategy. Older age was associated with bilateral salpingo-oophorectomy. Perioperative morbidity was acceptable. Evaluation of long-term effects and quality of life associated with endocrine ablation will help guide patient/provider decision-making.

INTRODUCTION

In 2020, an estimated 276 480 women will be diagnosed with breast cancer in the United States.[1] Approximately 85% of newly diagnosed breast cancers are hormone receptor positive,[2] 92% being potentially curable stage I–III disease.[3] Among women with hormone receptor positive breast cancer, 19–30% are younger than 50 years at the time of diagnosis.[3] Traditionally, premenopausal women were treated with tamoxifen for 5 years,[4] allowing a switch to an aromatase inhibitor if a postmenopausal state was reached. This changed following the SOFT and TEXT trial results,[5 6] published in 2014. Especially in premenopausal women who had undergone adjuvant chemotherapy due to high-risk features, adding an aromatase inhibitor with ovarian suppression resulted in significant improvement in disease-free survival (71.4% tamoxifen alone vs 80.4% exemestane plus ovarian suppression).[7] Bui and colleagues performed a systematic Cochrane review and meta-analysis that included 15 earlier trials to evaluate the effects of ovarian ablation for the treatment of premenopausal women with hormone receptor positive breast cancer.[8] The authors found evidence to support the addition of ovarian ablation in this patient population, with persisting benefit compared with observation, or when added to tamoxifen, or when added to chemotherapy and tamoxifen.

Bilateral salpingo-oophorectomy is an accepted alternative to medical ovarian suppression,[9] but is

irreversible. Due to current recommendations,[10 11] premenopausal women with high-risk features commit to ovarian ablation and prolonged endocrine therapy. Ovarian function can be suppressed either with gonadotrophin-releasing hormone agonists (GnRHa) goserelin, leuprolide, or triptorelin administered subcutaneously monthly or 3-monthly, by ovarian irradiation, or surgical bilateral salpingo-oophorectomy.[10] Because of the resulting implications for fertility and family planning, some patients may choose definitive surgical ablation. However, data are lacking about use and timing of therapeutic bilateral salpingo-oophorectomy. We sought to evaluate the patient, disease, and treatment characteristics of premenopausal women undergoing bilateral salpingo-oophorectomy, compared with women receiving medical ovarian suppression, as part of adjuvant treatment of hormone receptor positive breast cancer. This information will provide an insight into the current use of bilateral salpingo-oophorectomy in this population, and may improve patient/provider decision-making.

METHODS

Database and patient selection

This study was approved by our institutional review board. We performed a retrospective review of a prospective institutional breast cancer database, identifying all premenopausal women with hormone receptor positive (estrogen or progesterone receptor >1%) breast cancer diagnosed between January 2010 and December 2014 who underwent mastectomy or breast conserving surgery and either neoadjuvant or adjuvant medical treatment. Premenopausal status was determined by the clinician at initial consult and was defined by regular menses without exogenous hormones before treatment initiation. This period was chosen to capture all patients undergoing bilateral salpingo-oophorectomy in the first 5 years of adjuvant treatment. Clinical, pathological, and treatment variables were collected; 3321 women were identified (Figure 1). Any malignant histology was included and assigned to one of five categories: any ductal no lobular; any lobular no ductal; both lobular and ductal; inflammatory; other. Women who did not undergo breast surgery, presented more than 90 days from initial diagnosis, who had stage IV disease, or a known *BRCA* mutation, or insufficient documentation were excluded. A total of 2740 premenopausal women with stage I–III were included in the final analysis and assigned to the following groups: group 1, no endocrine therapy; group 2, endocrine therapy without ovarian suppression; group 3, endocrine therapy with medical ovarian suppression; or group 4, endocrine treatment with bilateral salpingo-oophorectomy at any time point. Patients receiving medical ovarian suppression (leuprorelin or goserelin) at any point during adjuvant treatment were assigned to group 3 unless ovarian suppression was started after a recurrence or a bilateral salpingo-oophorectomy was performed. Women undergoing bilateral salpingo-oophorectomy after documented relapse, progression of disease, or for other reasons (adnexal mass, ovarian cancer, uterine cancer) were not classified in group 4 for the primary diagnosis; instead these patients were assigned to groups 1–3 irrespective of the endocrine treatment they had received prior to recurrence.

For bilateral salpingo-oophorectomy, gynecological oncologists were consulted and minimally invasive surgery was the preferred method. Surgical details and complications were extracted from

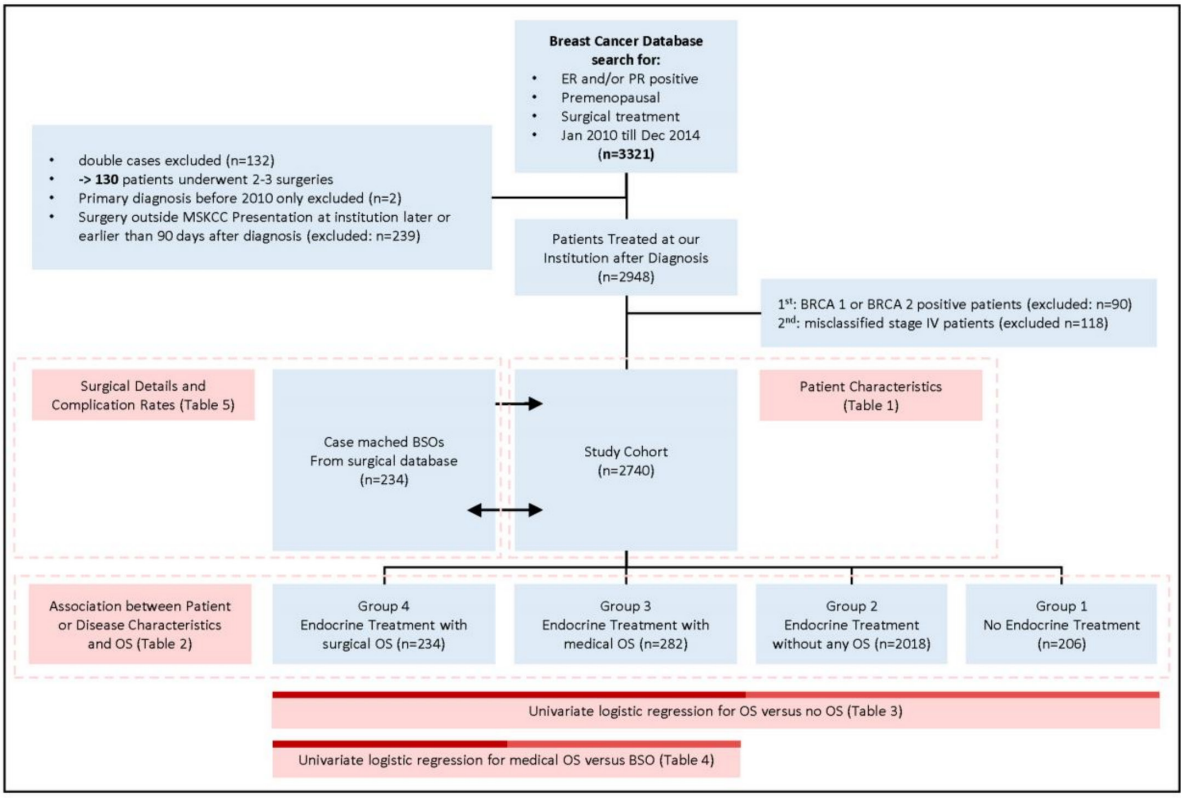

Figure 1 Study cohort selection. BSO, bilateral salpingo-oophorectomy; ER, estrogen receptor; OS, ovarian suppression; PR, progesterone receptor.

Table 1 Patient and disease characteristics (n=2740)

	n	%
Age at diagnosis		
Median (mean)	45 (43.8)	
Range	20–60	
IQR	40–48	
Year of diagnosis		
2010	530	19.3
2011	537	19.6
2012	498	18.2
2013	597	21.8
2014	578	21.1
Family history*		
No	1218	45.7
Yes	1445	54.3
Unknown	77	
Live children		
No	749	27.3
Yes	1991	72.7
Histology		
Any ductal no lobular	2188	79.9
Any lobular no ductal	268	9.8
Lobular and ductal	176	6.4
Inflammatory	12	0.4
Other	96	3.5
Grade*		
G1	196	7.8
G2	631	25.0
G3	1694	67.2
Unknown	219	
LN pos exact*		
No	1746	63.8
Yes	991	36.2
Unknown	3	
Stage*		
I	1377	54.4
II	846	33.4
III	307	12.2
Unknown	210	
Chemotherapy		
No	1020	37.2
Yes	1720	62.8
HER-2 targeted therapy		
None	2306	84.2
Trastuzumab	328	12.0
Trastuzumab+other	106	3.9
Any endocrine treatment		
No	213	7.8
Yes	2527	92.2
BSO		
None	2506	91.5
Yes	234	8.5
Medical OS		
None	2458	89.7
Yes	282	10.3

*For these variables, the unknowns are not considered in the percentage reporting.
BSO, bilateral salpingo-oophorectomy; HER-2, human epidermal growth factor receptor 2; IQR, interquartile range; LN, lymph node; OS, ovarian suppression.

the gynecological oncology surgical database. Complications were recorded and graded on a 1–5 scale according to a previously published classification system.[12]

Statistical analysis

Association between the treatment groups and patient or disease characteristics was assessed using the χ^2 test/Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables. Two sets of univariate logistic regression analyses were performed to identify predictors among patient and tumor characteristics. The first regression analysis compared women undergoing any type of ablation (medical ovarian suppression and bilateral salpingo-oophorectomy) with those who did not. A multivariate logistic model was created, based on all the variables with p less than 0.05 in univariate analysis. The second regression analysis was performed among all ovarian ablation patients, comparing those receiving medical ovarian suppression versus bilateral salpingo-oophorectomy. Microsoft Excel was used for data collection, SAS9.4 for statistical analyses.

RESULTS

Patient demographics

The final cohort comprised 2740 premenopausal women with a primary diagnosis of hormone receptor positive breast cancer during the study period, with median follow-up of 62.2 months (IQR 47.7–81.1) (Table 1). Median age was 45 years (IQR 40–48). Half (n=1445; 54%) of the study cohort had a family history of breast cancer. Most (n=1991; 73%) had children at the time of diagnosis. Most cancers were ductal histology (n=2188; 80%), poorly differentiated (tumor grade 3; n=1694; 67%). One-third (n=991; 36%) of women had lymph node involvement. The majority were diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage I (n=1377; 54%) or II (n=846; 33%) disease; 307 (12%) with stage III. Most received adjuvant or neoadjuvant chemotherapy (n=1720; 63%), adjuvant endocrine therapy (n=2527; 92%), or human epidermal growth factor receptor (HER-2) targeted treatments (n=434; 16%). Of 516 receiving ovarian ablation, 234 (45%) had bilateral salpingo-oophorectomy and 282 (55%) underwent medical ovarian suppression.

Table 2 Distribution of patients and disease characteristics between treatment groups

	No endocrine treatment (n=206)	Endocrine treatment without OS (n=2018)	Endocrine treatment with medical OS (n=282)	Endocrine treatment with BSO (n=234)	
	n (%)	n (%)	n (%)	n (%)	P value
Follow-up					
Median	37.1	64.1	60.1	67.3	
Range	0.6–105.9	0.5–115.1	3.1–108.3	6.2–108.4	
IQR	7.5–58.2	48.9–82.7	49.2–77.7	51.9–84.4	
Age at diagnosis					
Median (mean)	45 (43.9)	45(44)	43 (42.2)	45 (44.1)	<0.001*
Range	20–56	20–60	24–59	26–55	
IQR	41–48	40–49	37–48	40–48	
Year of diagnosis					
2010	40 (7.5)	404 (76.2)	41 (7.7)	45 (8.5)	<0.001
2011	31 (5.8)	421 (78.4)	39 (7.3)	46 (8.6)	
2012	37 (7.4)	373 (74.9)	46 (9.2)	42 (8.4)	
2013	42 (7)	442 (74)	69 (11.6)	44 (7.4)	
2014	56 (9.7)	378 (65.4)	87 (15.1)	57 (9.9)	
Family history†					
No	85 (7)	922 (75.7)	116 (9.5)	95 (7.8)	0.202
Yes	114 (7.9)	1041 (72)	157 (10.9)	133 (9.2)	
Unknown	7	55	9	6	
Live children					
No	62 (8.3)	556 (74.2)	79 (10.5)	52 (6.9)	0.263
Yes	144 (7.2)	1462 (73.4)	203 (10.2)	182 (9.1)	
Histology					
Any ductal no lobular	166 (7.6)	1606 (73.4)	232 (10.6)	184 (8.4)	0.008
Any lobular no ductal	19 (7.1)	190 (70.9)	34 (12.7)	25 (9.3)	
Lobular and ductal	8 (4.5)	135 (76.7)	11 (6.3)	22 (12.5)	
Inflammatory	0 (0)	9 (75)	2 (16.7)	1 (8.3)	
Other	13 (13.5)	78 (81.3)	3 (3.1)	2 (2.1)	
Grade†					
G1	27 (13.8)	155 (79.1)	7 (3.6)	7 (3.6)	<0.001
G2	35 (5.5)	478 (75.8)	72 (11.4)	46 (7.3)	
G3	113 (6.7)	1229 (72.6)	186 (11)	166 (9.8)	
Unknown	31	156	17	15	
LN pos exact†					
No	163 (9.3)	1319 (75.5)	141 (8.1)	123 (7)	<0.001
Yes	43 (4.3)	698 (70.4)	140 (14.1)	110 (11.1)	
Unknown		1	1	1	
Stage (unknown removed)					
I	135 (9.8)	1048 (76.1)	107 (7.8)	87 (6.3)	<0.001
II	47 (5.6)	634 (74.9)	86 (10.2)	79 (9.3)	
III	16 (5.2)	193 (62.9)	55 (17.9)	43 (14)	
Chemotherapy					
No	138 (13.5)	729 (71.5)	88 (8.6)	65 (6.4)	<0.001
Yes	68 (4)	1289 (74.9)	194 (11.3)	169 (9.8)	
HER-2 targeted					

Continued

Table 2 Continued

	No endocrine treatment (n=206)	Endocrine treatment without OS (n=2018)	Endocrine treatment with medical OS (n=282)	Endocrine treatment with BSO (n=234)	
	n (%)	n (%)	n (%)	n (%)	P value
None	183 (7.9)	1698 (73.6)	242 (10.5)	183 (7.9)	<0.001
Trastuzumab	17 (5.2)	256 (78)	25 (7.6)	30 (9.1)	
Trastuzumab+other	6 (5.7)	64 (60.4)	15 (14.2)	21 (19.8)	

Percentages are calculated by row.
*p values for continuous variables are calculated using Kruskal-Wallis test, if not otherwise labeled.
†For these variables the unknowns are not considered in the percentage reporting and the test for p value.
BSO, bilateral salpingo-oophorectomy; HER-2, human epidermal growth factor receptor 2; IQR, interquartile range; LN, lymph node; OS, ovarian suppression.

Distribution of treatment groups

Patients were assigned to four groups (Table 2): roup 1 (n=206; 11%), no endocrine treatment; group 2 (n=2018; 74%), any endocrine treatment without ovarian ablation; group 3 (n=282; 10%), any endocrine treatment with medical ovarian suppression; or group 4 (n=234; 9%), therapeutic bilateral salpingo-oophorectomy at any time during primary treatment. Median follow-up for women receiving endocrine treatment without or with ovarian suppression (groups 2 and 3) was 64.1 (IQR 48.9–82.7) and 60.1 (IQR 49.2–77.7) months, respectively. Median follow-up for women undergoing bilateral salpingo-oophorectomy was 67.3 months (IQR 51.9–84.4).

Table 3 Univariate logistic regression for patients undergoing endocrine treatment without ovarian ablation (group 1 and group 2: n=2224) versus with ovarian ablation (group 3 and group 4: n=516)

Variables	Levels	OR	95% CI lower bounds	95% CI upper bounds	p value
Age at diagnosis	As one year increase	0.975	0.961	0.990	**0.001**
Year of diagnosis	2011 vs 2010	0.971	0.700	1.347	**<0.001**
	2012 vs 2010	1.108	0.800	1.535	
	2013 vs 2010	1.205	0.885	1.641	
	2014 vs 2010	1.713	1.271	2.308	
Family history (77 unknown)	Yes vs no	1.198	0.985	1.458	0.071
Live children	Yes vs no	1.131	0.909	1.408	0.271
Histology	Lobular no ductal vs ductal no lobular	1.202	0.884	1.636	**0.019**
	Lobular and ductal vs ductal no lobular	0.983	0.663	1.457	
	Inflammatory vs ductal no lobular	1.420	0.383	5.268	
	Other vs ductal no lobular	0.234	0.095	0.579	
Grade (219 unknown)	G2 vs G1	2.988	1.674	5.331	**<0.001**
	G3 vs G1	3.407	1.954	5.940	
LN pos exact (3 unknown)	Yes vs no	1.894	1.560	2.300	**<0.001**
Stage (210 unknown)	II vs I	1.477	1.176	1.856	**<0.001**
	III vs I	2.859	2.153	3.798	
Chemotherapy	Yes vs no	1.516	1.232	1.865	**<0.001**
HER-2 targeted	Trastuzumab vs none	0.892	0.655	1.214	**<0.001**
	Trastuzumab+other vs none	2.276	1.502	3.449	

The OR is modeled for ovarian suppression (OS)=yes. OR>1 means more likely to get OS; OR<1 less likely to get OS. Unknown=number of patients in analysis who did not have documentation for this variable.
Bold p values represent p values of significance.
HER-2, human epidermal growth factor receptor 2; LN, lymph node; OS, ovarian suppression.

Table 4 Univariate logistic regression for patients undergoing bilateral salpingo-oophorectomy (n=234) versus ovarian suppression (n=282) for ovarian ablation

Variables	Levels	OR	95% CI lower bounds	95% CI upper bounds	p value
Age at diagnosis	As one year increase	1.051	1.021	1.082	**<0.001**
Year of diagnosis	2011 vs 2010	1.075	0.589	1.960	0.082
	2012 vs 2010	0.832	0.459	1.508	
	2013 vs 2010	0.581	0.329	1.025	
	2014 vs 2010	0.597	0.348	1.023	
Family history (15 unknown)	Yes vs no	1.034	0.724	1.477	0.852
Live children	Yes vs no	1.362	0.910	2.038	0.133
Histology	Lobular no ductal vs ductal no lobular	0.927	0.534	1.609	0.176
	Lobular and ductal vs ductal no lobular	2.522	1.192	5.334	
	Inflammatory vs ductal no lobular	0.630	0.057	7.007	
	Other vs ductal no lobular	0.841	0.139	5.083	
Grade (32 unknown)	G2 vs G1	0.639	0.210	1.941	0.286
	G3 vs G1	0.892	0.307	2.598	
LN pos exact (2 unknown)	Yes vs No	0.901	0.636	1.275	0.556
Stage (59 unknown)	II vs I	1.130	0.745	1.713	0.777
	III vs I	0.962	0.590	1.568	
Chemotherapy	Yes vs no	1.179	0.806	1.727	0.396
HER-2 targeted	Trastuzumab vs none	1.587	0.902	2.790	0.076
	Trastuzumab+other vs none	1.851	0.929	3.691	

The OR is modeled for BSO yes, as OR>1 means more likely to get BSO, OR<1 less likely to get BSO. Unknown=number of patients in analysis who did not have documentation for this variable.
Bold p values represent p values of significance.
BSO, bilateral salpingo-oophorectomy; HER-2, human epidermal growth factor receptor 2; LN, lymph node; OS, ovarian suppression.

Neither family history of breast cancer nor history of giving birth to one or more children showed an association with any treatment group. All other characteristics—histological subtype, lymph node status, tumor grade, chemotherapy, HER-2 targeted treatment, age at diagnosis—were unevenly distributed between the groups.

Factors associated with ovarian suppression

Univariate logistic regression was performed (Table 3). Women who did not receive ovarian ablation (group 1—no endocrine, group 2—endocrine without ovarian suppression) were pooled and compared with those undergoing either medical ovarian suppression or bilateral salpingo-oophorectomy (group 3—ovarian suppression, group 4—bilateral salpingo-oophorectomy). Younger age (OR 0.98; 95% CI 0.96 to 0.99; p=0.001), more recent diagnosis (2014 vs 2010; OR 1.71; 95% CI 1.27 to 2.31; p<0.001), higher-grade tumors (grade 3 vs 1: OR 3.41; 95% CI 1.95 to 5.95; grade 2 vs 1: OR 2.99; 95% CI 1.67 to 5.33; p<0.001), lymph node involvement (OR 1.89; 95% CI 1.56 to 2.30; p<0.001), higher FIGO stage (stage II vs I: OR 1.48; 95% CI 1.18 to 1.86; stage III vs I: OR 2.86; 95% CI 2.15 to 3.80), uncommon histology (other vs ductal: OR 0.23; 95% CI 0.10 to 0.58; p=0.019), or chemotherapy (OR 1.52; 95% CI 1.23 to 1.87; p<0.001) were associated with likelihood of either medical ovarian suppression or bilateral salpingo-oophorectomy. Positive family history, and children, were not associated with ovarian ablation.

A multivariate model using all patient and disease characteristics showed significance on univariate analyses (online supplemental table S1). With existence of other covariates in the same model, only more recent year of diagnosis (2014 vs 2010; OR 1.557; 95% CI 1.11 to 2.24), higher stage (stage III vs I: OR 2.26; 95% CI 1.37 to 3.72), and HER-2 treatment (trastuzumab plus other vs no HER-2 targeting; OR 2.39; 95% CI 1.342 to 4.231) were significantly associated with medical ovarian suppression or bilateral salpingo-oophorectomy.

A subgroup analysis was performed for all women receiving ovarian ablation, comparing group 3—ovarian suppression versus group 4—bilateral salpingo-oophorectomy (Table 4). Older age at diagnosis (1.05; 95% CI 1.02 to 1.08; p<0.001) was associated with higher likelihood of bilateral salpingo-oophorectomy. For all other patient and

Table 5 Surgical details and complication rates of bilateral salpingo-oophorectomy in the study cohort

	n	%
All BSO	234	
Admission		
Inpatient	33	14.7
Outpatient	192	85.3
Surgery type		
Laparoscopy	152	66.7
Laparotomy	14	6.1
Robotic	62	27.2
Concomitant surgery	89	38.9
Breast surgery	46	20.1
Hysterectomy	35	15.3
Other surgery	24	10.5
BSO with and without concomitant surgery (n=234)		
Readmission	4	1.8
Complications	12	5.4
Surgery duration (min)		
Median (mean)	95 (112.1)	
Range	18–647	
IQR	53.2–145.8	
EBL (mL)		
Median (mean)	20 (41.5)	
Range	0–1000	
IQR		
Hospitalization (days)		
Median (mean)	0 (0.5)	
Range	0–7	
IQR	0–0	
Comorbidity*	52	23.3
BSO without concomitant surgery (n=145)		
Readmission	1	0.7
Complications	2	1.5
Surgery duration (min)		
Median (mean)	62 (71.4)	
Range	18–185	
IQR	40–92	
EBL (mL)		
Median (mean)	20 (24.8)	
Range	0–300	
IQR		
Hospitalization (days)		
Median (mean)	0 (0.1)	
Range	0–1	
IQR	0–0	
Comorbidity*	32	23.7

Missing variables are not included in the percentage denominators.
*Comobidity includes at least one incidence of 'hypothyroidism', 'arterial hypertension', 'heart disease', 'pulmonary embolism or DVT' or 'diabetes'.
BSO, bilateral salpingo-oophorectomy; EBL, estimated blood loss; IQR, interquartile range.

disease characteristics there were no significant differences in distribution between bilateral salpingo-oophorectomy and medical ovarian suppression.

In total, 335 women started medical ovarian suppression; 53 of these underwent bilateral salpingo-oophorectomy later. When comparing these 53 with the 282 who received only medical ovarian suppression, older age was the only factor associated with bilateral salpingo-oophorectomy (p=0.035).

Timing of ovarian ablation

Endocrine treatment began after a median of 6.7 months (IQR 4.3–8.6) in all three treatment groups (group 2: 6.8, IQR 4.4–8.7; group 3: 6.3 months, IQR 3.7–8.3; group 4: 6.6 months, IQR 3.8–8.4). Median time from diagnosis to any type of ovarian suppression was 12.4 months (IQR 64–28.4) (online supplemental table S2).

In group 3, 119 women started endocrine therapy and medical ovarian suppression at the same time; 135 had medical ovarian suppression after a median endocrine treatment time of 13.6 months (IQR 4–34). Median time from diagnosis to bilateral salpingo-oophorectomy was 22.9 months (IQR 13.5–37.7). Most women undergoing bilateral salpingo-oophorectomy (n=193, 93%) received endocrine therapy without medical ovarian suppression for a median of 18.3 months (IQR 9.4–34.7) before bilateral salpingo-oophorectomy. Of 234 patients undergoing bilateral salpingo-oophorectomy, 53 (22%) started medical ovarian suppression and had bilateral salpingo-oophorectomy later. For women crossing over to bilateral salpingo-oophorectomy, median time from first administration of medical ovarian suppression to bilateral salpingo-oophorectomy was 11.7 months (IQR 5.95–22.8).

Complications of surgical ovarian ablation

The majority (n=192, 85%) underwent outpatient surgery (Table 5); 33 (15%) had inpatient surgery. Median length of hospitalization was 0 (range 0–7). Most surgeries were laparoscopically (n=152, 67%) or robotically assisted (n=62, 27%); 14 (6%) were laparotomies. All laparotomies included additional abdominal procedures at the time of bilateral salpingo-oophorectomy. Eighty-nine women (39%) undergoing bilateral salpingo-oophorectomy had concomitant surgical procedures, including breast reconstruction (46, 20%), hysterectomy (35, 15%), hernia repair, vulvar surgery, or additional intraabdominal resections (24, 11%). Twelve (5%) had postoperative complications with four readmissions. Among those undergoing bilateral salpingo-oophorectomy without concomitant surgery, 2 (1.5%) had complications with one readmission. Grade 1 complications were documented in two patients: one urinary tract infection after laparoscopic bilateral salpingo-oophorectomy, and one postoperative wound infection and seroma after laparotomy for total abdominal hysterectomy/bilateral salpingo-oophorectomy in a patient with diabetes. Grade 2 complications included a wound infection requiring readmission for intravenous antibiotics after laparoscopic bilateral salpingo-oophorectomy with concomitant breast surgery, and symptomatic anemia requiring transfusion after robotic-assisted total laparoscopic hysterectomy/bilateral salpingo-oophorectomy. One patient was readmitted for a grade 3 pelvic hematoma requiring drainage; she had a history of peritonitis with adhesions, requiring conversion to laparotomy with enterolysis for bilateral salpingo-oophorectomy.

Median duration of surgery was 95 min (IQR 53.2–145.8). Eighty-four (38%) patients had an operative time greater than 120 min. Twenty-five (11%) had an operative time greater than 180 min; in 24 of these 25, combined surgical procedures were performed. Median blood loss was 20 mL (range 0–1000). Among women undergoing bilateral salpingo-oophorectomy only, median surgical duration was 62 min (IQR 40–92); 16 (12%) exceeded 120 min.

DISCUSSION

In this study, we assessed the characteristics of premenopausal women undergoing surgical ovarian ablation compared with women receiving medical ovarian suppression for hormone receptor positive breast cancer at our institution. Of 2740 women identified, 516 (19%) were treated with medical or surgical ovarian ablation. Those selected for ovarian ablation presented with high-risk tumor features (higher tumor grade or stage, lymph node involvement), or were younger at the time of diagnosis. Among those selected for ovarian ablation, older age was associated with bilateral salpingo-oophorectomy. We detected a delayed induction of ovarian suppression therapy in a large proportion of women in both the medical ablation (13.6 months) and the bilateral salpingo-oophorectomy (22.9 months) treatment groups. Surgical complications were few, even with combined surgical procedures.

The landscape of adjuvant endocrine therapy in premenopausal women has changed significantly since the joint analysis of the SOFT and TEXT trials.[7] These data had a median follow-up of 8 years, with findings suggesting an overall survival benefit of 1.8% for women receiving tamoxifen plus ovarian suppression versus tamoxifen alone (HR 0.59; 95% CI 0.42 to 0.84). This group was characterized by high-risk clinicopathological features and younger age (median 40 years). The absolute benefits of ovarian suppression were prominent in women who remained premenopausal after chemotherapy. Among those patients the rate of disease-free survival observed with tamoxifen plus ovarian suppression was 5.3% higher than tamoxifen alone and 9% higher with exemestane plus ovarian suppression. Our dataset presents similar distribution of high-risk features among women undergoing ovarian suppression. This may be related to the clinical conduct adopted by the specialists after the results of the SOFT and TEXT trial. Within the cohort undergoing ovarian ablation, the association of older age (OR 1.05) and bilateral salpingo-oophorectomy was significant. We hypothesize that women of older age are more inclined to consider surgical ovarian suppression.

In the combined analysis of TEXT and SOFT trials, the addition of ovarian suppression was associated with a substantial increase in grade 3 adverse events: 24.6% for tamoxifen versus 31.0% for tamoxifen plus ovarian suppression vs 32.3% for exemestane plus ovarian suppression. A similar increase was recorded for musculoskeletal symptoms (6.7% vs 5.7% vs 11.4%) and osteoporosis (3.9% vs 7.2 vs 14.8%), respectively. Vaginal dryness and dyspareunia were most frequent in the ovarian suppression plus exemestane group. Adverse events specifically for patients who opted for bilateral salpingo-oophorectomy or ovarian irradiation were not presented.

While optimal duration of ovarian suppression is not known, a postmenopausal state in young women comes with significant morbidity. In the Nurses' Health Study, in the cohort undergoing hysterectomy between ages 35 and 50 without estrogen replacement therapy, the addition of bilateral salpingo-oophorectomy resulted in a significant increase in all-cause mortality.[13] Long-term morbidity data are not available for medical ovarian suppression; however, it can be assumed that women treated with medical ovarian suppression and aromatase inhibitor would encounter long-term effects similar to those of premenopausal women undergoing bilateral salpingo-oophorectomy. Applying both the benefits of ovarian suppression for breast cancer prognosis and the resulting morbidity to a Markov Monte Carlo simulation model, Kwon and colleagues estimated 577 and 787 additional deaths in the medical ovarian suppression and bilateral salpingo-oophorectomy groups, respectively.[14] When considering deaths from breast cancer and treatment-related adverse events, this model makes tamoxifen the optimal choice in endocrine therapy for premenopausal breast cancer; it is preferred for low-risk disease.

It is essential to identify candidates for ovarian suppression whose high risk of recurrence outweighs the risk of long-term morbidity. Regan and colleagues incorporated clinicopathological features in a continuous score termed 'composite risk'.[15 16] The absolute improvement of freedom from distant metastases for women with high composite risk was 10–15%. Although the composite risk score was not applied at our institution, women with high-risk features such as younger age, high tumor grade, stage III, or lymph node involvement were more likely to undergo medical ovarian suppression or bilateral salpingo-oophorectomy.

This retrospective study has limitations. As a single-institution study at a specialty center, the findings may reflect multidisciplinary care delivered by a relatively small number of clinicians; therefore, some findings may not be generalizable to other institutions. Menopausal status was extracted from physicians' charts at initial consult, not by objective hormone level measurements; thus, we were unable to differentiate between premenopausal and perimenopausal status. It is unclear how many women were perimenopausal at the time of diagnosis, or how many transitioned into menopause after chemotherapy. For this reason, we analyzed the distribution of women older than 50 years between the four treatment groups. The distributions were even, ranging from 8.3% to 12.7% in each group (data not shown). Our observed rate of bilateral salpingo-oophorectomy versus medical ovarian suppression is higher than those cited in the SOFT and TEXT trials (16–18% of patients assigned to ovarian suppression opted to undergo bilateral oophorectomy or bilateral ovarian irradiation).[7] In our cohort, the majority of women seeking bilateral salpingo-oophorectomy did so before initiating medical ovarian suppression. Many (n=193, 93%) began tamoxifen for a median duration of 18 months before crossing over to bilateral salpingo-oophorectomy. Women enrolled in the SOFT trial were offered a choice of medical ovarian suppression, bilateral salpingo-oophorectomy, or ovarian irradiation. Medical ovarian suppression was preferred (91%). In the TEXT trial, bilateral salpingo-oophorectomy or ovarian irradiation was allowed after 6 months of medical ovarian suppression. The rate of early cessation of medical ovarian suppression without substitution of ovarian ablation was 19% in the combined population of SOFT and TEXT. The prognostic impact of discontinuing medical ovarian suppression is unclear. In our study, only 53 women (22%) who had bilateral salpingo-oophorectomy started with medical ovarian

suppression. The higher rate of bilateral salpingo-oophorectomy may be a result of the time period during which medical ovarian suppression for premenopausal women was not yet fully established. Another limitation is the lack of specific reasons cited for different forms of ovarian ablation; detailed information regarding the decision-making processes about bilateral salpingo-oophorectomy, or discussions about alternatives, were often not specified in physicians' notes. Future research should examine whether adverse events associated with endocrine therapy, and/or quality of life concerns (ie, time commitment, mood disturbance) associated with medical ovarian suppression impact choice. There is a paucity of data regarding postoperative satisfaction or regret in women choosing bilateral salpingo-oophorectomy. This information would be crucial in guiding discussions between patients and providers regarding treatment options.

The only direct comparison of bilateral salpingo-oophorectomy versus treatment with luteinizing hormone-releasing hormone agonists was performed in women with metastatic disease. The authors show similar progression-free and overall survival in both groups.[17] Bilateral salpingo-oophorectomy in the adjuvant setting was tested prior to that study and was shown to be equivalent to cyclophosphamide, methotrexate, and fluorouracil when combined with tamoxifen[18]; a second analysis 10 years later yielded similar results.[19] The E-3193 study randomized 337 women to tamoxifen with and without ovarian suppression, with most choosing to undergo bilateral salpingo-oophorectomy (n=74; 42%). Neither quality of life nor complication rates differed between the groups.[20] The adequacy of maintaining estrogen level suppression was examined in the SORT-EST substudy; at 3, 6, and 12 months, 34.2% of 79 treated with ovarian suppression and exemestane demonstrated at least one E2 level greater than 2.72 pg/mL.[21] It is unclear whether these small transient increases of estradiol levels are also present, but less likely, in women undergoing bilateral salpingo-oophorectomy. In a recent study, Ferrandina and colleagues analyzed the cost-effectiveness of laparoscopic bilateral salpingo-oophorectomy and GnRHa administration in patients aged 40–49 years with hormone-sensitive breast cancer through a probabilistic decision tree model.[22] The authors concluded that bilateral salpingo-oophorectomy is more cost-effective than GnRHa in the adjuvant setting.

CONCLUSION

Ovarian ablation is known to improve survival in premenopausal women with hormone receptor positive breast cancer with high-risk features. Therapeutic bilateral salpingo-oophorectomy is associated with low morbidity and is a reasonable alternative to medical ovarian suppression. However, many questions remain. Future prospective studies addressing the decision-making process, patients' treatment preferences, and long-term effects of endocrine ablation are needed. Patient-reported outcomes, health-related quality of life, investigation of provider factors, treatment considerations and choice—including postoperative satisfaction or regret—will help guide future discussions between patients and providers, facilitating more informed decisions about treatment.

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REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7–30.
2 Kohler BA, Sherman RL, Howlader N, *et al*. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by Race/Ethnicity, poverty, and state. *J Natl Cancer Inst* 2015;107:djv048.
3 Howlader N, Altekruse SF, Li CI, *et al*. Us incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. *J Natl Cancer Inst* 2014;106. doi:10.1093/jnci/dju055. [Epub ahead of print: 28 Apr 2014].
4 , Davies C, Godwin J, *et al*, Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;378:771–84.
5 Francis PA, Regan MM, Fleming GF, *et al*. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015;372:436–46.
6 Pagani O, Regan MM, Walley BA, *et al*. Adjuvant exemestane with ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014;371:107–18.
7 Francis PA, Pagani O, Fleming GF, *et al*. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med* 2018;379:122–37.
8 Bui KT, Willson ML, Goel S, *et al*. Ovarian suppression for adjuvant treatment of hormone receptor-positive early breast cancer. *Cochrane Database Syst Rev* 2020;3.
9 (NCCN©) NCCN: Breast Cancer - Version 6.2020. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®):MS-33 2020.
10 Burstein HJ, Lacchetti C, Anderson H, *et al*. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of clinical oncology clinical practice guideline update on ovarian suppression. *J Clin Oncol* 2016;34:1689–701.
11 Paluch-Shimon S, Cardoso F, Partridge AH, *et al*. ESO-ESMO 4th International consensus guidelines for breast cancer in young women (BCY4). *Ann Oncol* 2020.
12 Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.
13 Parker WH, Feskanich D, Broder MS, *et al*. Long-Term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. *Obstet Gynecol* 2013;121:709–16.
14 Kwon JS, Pansegrau G, Nourmoussavi M, *et al*. Long-Term consequences of ovarian ablation for premenopausal breast cancer. *Breast Cancer Res Treat* 2016;157:565–73.
15 Regan MM, Francis PA, Pagani O, *et al*. Absolute improvements in freedom from distant recurrence with adjuvant endocrine therapies for premenopausal women with hormone receptor-positive (HR+) HER2-negative breast cancer (bc): results from text and soft. *JCO* 2018;36:503
16 Regan MM, Francis PA, Pagani O, *et al*. Absolute benefit of adjuvant endocrine therapies for premenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-Negative early breast cancer: text and soft trials. *J Clin Oncol* 2016;34:2221–31.
17 Taylor CW, Green S, Dalton WS, *et al*. Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. *J Clin Oncol* 1998;16:994–9.
18 Nomura Y, Tashiro H, Hisamatsu K, *et al*. A randomized trial of adjuvant endocrine therapy, chemotherapy, and chemoendocrine therapy for operable breast cancer stratified by estrogen receptors. *Cancer* 1988;61:2168–75.
19 Nomura Y, Shirouzu M, Takayama T. Direct comparisons of adjuvant endocrine therapy, chemotherapy, and chemoendocrine therapy for operable breast cancer patients stratified by estrogen receptor and menopausal status. *Breast Cancer Res Treat* 1998;49:51–60.
20 Tevaarwerk AJ, Wang M, Zhao F, *et al*. Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node-negative, hormone receptor-positive breast cancer (E-3193, INT-0142): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2014;32:3948–58.
21 Bellet M, Gray KP, Francis PA, *et al*. Twelve-Month estrogen levels in premenopausal women with hormone receptor-positive breast cancer receiving adjuvant Triptorelin plus exemestane or tamoxifen in the suppression of ovarian function trial (soft): the SOFT-EST substudy. *J Clin Oncol* 2016;34:1584–93.
22 Ferrandina G, Amadio G, Marcellusi A, *et al*. Bilateral salpingo-oophorectomy versus GnRH analogue in the adjuvant treatment of premenopausal breast cancer patients: cost-effectiveness evaluation of breast cancer outcome, ovarian cancer prevention and treatment. *Clin Drug Investig* 2017;37:1093–102.

Table S1: Multivariate Logistic Model for Patients Undergoing Endocrine Treatment Without Ovarian Ablation (Group 1 and Group 2: *n*= 2224) versus With Ovarian Ablation (Group 3 and Group 4: *n*=516).

Variables	Levels	OR	95% CI Lower Bounds	95% CI Upper Bounds	*p*-value
Age at Diagnosis	as 1 yr increase	0.988	0.971	1.006	0.181
Year of Diagnosis	2011 vs 2010	0.979	0.677	1.416	**0.037**
	2012 vs 2010	1.128	0.780	1.631	
	2013 vs 2010	1.081	0.761	1.538	
	2014 vs 2010	1.577	1.109	2.242	
Histology	Lobular no ductal vs Ductal no lobular	1.409	0.902	2.201	0.085
	Lobular and ductal vs Ductal no lobular	0.955	0.625	1.46	
	Inflammatory vs Ductal no lobular	0.646	0.162	2.571	
	Other vs Ductal no lobular	0.253	0.078	0.823	
Grade (219 unk.)	G2 vs G1	1.917	1.053	3.493	0.058
	G3 vs G1	2.037	1.136	3.652	
LN Pos Exact (3 unk.)	Yes vs. No	1.178	0.799	1.739	0.408
Stage (210 unk.)	II vs. I	1.226	0.846	1.778	**<0.001**
	III vs. I	2.259	1.372	3.72	
Chemotherapy	Yes vs. No	0.969	0.726	1.292	0.829
HER-2 Targeted	Trastuzumab vs. None	0.797	0.551	1.152	**0.004**
	Trastuzumab+Other vs. None	2.382	1.342	4.231	

All the variables which had univariate p-value significant ($p<0.05$) were entered into this multivariate model. The Odds Ratio (OR) is modeled for ovarian suppression (OS) = yes. OR>1 means more likely to get OS; OR<1 less likely to get OS; unk., unknown: number of patients in analysis who did not have documentation for this variable. All the unk. were excluded from this model building. The actual number in each group was *N*=426 vs. *N*=1893. LN, lymph node

Table S2: Timing of Endocrine Therapy: Medical Ovarian Suppression and Bilateral Salpingo-oophorectomy Among the Three Endocrine Treatment Groups

	Group 2 **Endocrine Treatment without OS (*n*=2018)**	Group 3 **Endocrine Treatment with medical OS (*n*=282)**	Group 4 **Endocrine Treatment with BSO (*n*=234)**
Months from Diagnosis to Start Endocrine treatment (without OS or BSO)			
Median (Mean)		6.7(6.7)	
Range		0.2-42.3	
IQR		4.3-8.6	
Median (Mean)	6.8(6.8)	6.3(6.5)	6.6(6.4)
Range	0.2-42.3	0.5-33.6	0.6-18.3
IQR	4.4-8.7	3.7-8.3	3.8-8.4
Missing start date	107	26	19
Patients treated with both, endocrine treatment* and OS or BSO	0 (0%)	256	208
Months from Diagnosis to any type of OS			
Median (Mean)	-	12.4(19.7)	
Range	-	0.76 - 94.0	
IQR	-	6.4-28.4	
Months from Diagnosis to BSO			
Median (Mean)	-		22.9(27.2)
Range	-		0.9-90.3
IQR	-		13.5-37.7
Endocrine treatment* before medical (group 3) or BSO (group 4)	-	135(88.8%)	193(92.8%)
Endocrine treatment* started with medical OS or BSO	-	119(80.4%)	4(1.9%)
Medical OS or BSO started before endocrine treatment*	-	2(66.7%)	11(5.3%)
Months from Start of Endocrine treatment* to start of medical OS or BSO			
N	-	135	193
Median (Mean)	-	13.6(19.8)	18.3(23.4)
Range	-	0-89.8	0.9-88.2
IQR	-	4-34	9.4-34.7

* in this context "endocrine treatment" refers to treatment with either tamoxifen or aromatase inhibitor. OS, ovarian suppression; BSO, bilateral salpingo-oophorectomy; IQR, interquartile range