



Original Article

Surgical Findings and Outcomes in Premenopausal Breast Cancer Patients Undergoing Oophorectomy: A Multicenter Review From the Society of Gynecologic Surgeons Fellows Pelvic Research Network

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ABSTRACT **Study Objective:** To describe the procedures performed, intra-abdominal findings, and surgical pathology in a cohort of women with premenopausal breast cancer who underwent oophorectomy.

Design: Multicenter retrospective chart review (Canadian Task Force classification II-3).

Setting: Nine US academic medical centers participating in the Fellows' Pelvic Research Network (FPRN).

Patients: One hundred twenty-seven women with premenopausal breast cancer undergoing oophorectomy between January 2013 and March 2016.

Intervention: Surgical castration.

Measurements and Main Results: The mean patient age was 45.8 years. Fourteen patients (11%) carried a *BRCA* mutations, and 22 (17%) carried another germline or acquired mutation, including multiple variants of uncertain significance. There was wide variation in surgical approach. Sixty-five patients (51%) underwent pelvic washings, and 43 (35%) underwent concurrent hysterectomy. Other concomitant procedures included midurethral sling placement, appendectomy, and hysteroscopy. Three patients experienced complications (transfusion, wound cellulitis, and vaginal cuff dehiscence). Thirteen patients (10%) had ovarian pathology detected on analysis of the surgical specimen, including metastatic tumor, serous cystadenomas, endometriomas, and Brenner tumor. Eight patients (6%) had Fallopian tube pathology, including 3 serous tubal intraepithelial cancers. Among the 44 uterine specimens, 1 endometrial adenocarcinoma and 1 multifocal endometrial intraepithelial neoplasia were noted. Regarding the entire study population, the number of patients meeting our study criteria and seen by gynecologic surgeons in the FPRN for oophorectomy increased by nearly 400% from 2013 to 2015.

Conclusion: Since publication of the Suppression of Ovarian Function Trial data, bilateral oophorectomy has been recommended for some women with premenopausal breast cancer to facilitate breast cancer treatment with aromatase inhibitors.

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These women may be at elevated risk for occult abdominal pathology compared with the general population. Gynecologic surgeons often perform castration oophorectomy in patients with breast cancer as an increasing number of oncologists are using aromatase inhibitors to treat premenopausal breast cancer. Our data suggest that other abdominal/pelvic cancers, precancerous conditions, and previously unrecognized metastatic disease are not uncommon findings in this patient population. Gynecologists serving this patient population may consider a careful abdominal survey, pelvic washings, endometrial sampling, and serial sectioning of fallopian tube specimens for a thorough evaluation. *Journal of Minimally Invasive Gynecology* (2018) 25, 111–115 © 2017 AAGL. All rights reserved.

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Breast cancer is the most frequently diagnosed malignancy and the fourth-leading cause of death in women in the United States, with an estimated 252,710 new cases expected in 2017 [1]. Approximately 12% of women will be diagnosed with breast cancer at some point in life, and an estimated 19% of deaths from breast cancer occur in women under age 55 years [1].

In 2014, the results from the Suppression of Ovarian Function Trial (SOFT) were published. SOFT was a phase 3, randomized clinical trial of more than 3000 premenopausal women with breast cancer who were assigned to 1 of 3 treatment arms after breast surgery: tamoxifen as a single agent, tamoxifen plus ovarian suppression, or exemestane (an aromatase inhibitor) plus ovarian suppression. Ovarian suppression was accomplished with bilateral oophorectomy, ovarian irradiation, or triptorelin (a gonadotropin-releasing hormone [GnRH] agonist). Several conclusions were drawn from the results of this trial. First, the addition of ovarian suppression to tamoxifen offered no increase in disease free survival to the overall population. Second, sub-group analyses suggested a decrease in breast cancer recurrence for women with high-risk disease (those selected for chemotherapy due to clinico-pathologic features of their disease) who had undergone chemotherapy with ovarian suppression plus exemestane [2].

The SOFT was planned alongside the Tamoxifen and Exemestane Trial (TEXT), a randomized trial of more than 4000 premenopausal women with hormonally sensitive breast cancer randomized to either exemestane plus the GnRH agonist triptorelin or tamoxifen plus triptorelin [3]. A combined analysis of data from the SOFT and TEXT showed that in premenopausal women with hormone receptor–positive breast cancer, the combination of ovarian suppression plus exemestane therapy was associated with significantly improved disease-free survival at 5 years [4].

Owing to the dissemination of these data, breast oncologists are now recommending that some premenopausal women with high-risk disease undergo bilateral oophorectomy to augment treatment with aromatase inhibitors [5–7]. As this treatment regimen becomes more widespread, gynecologic surgeons likely will be requested to participate in the care of this patient population by performing castration oophorectomy [8]. Here we describe current practice patterns of gynecologic surgeons involving this population.

The intra-abdominal evaluation done at the time of bilateral oophorectomy offers an opportunity to determine the prevalence of occult pathology. Our objective in this study

was to describe intra-abdominal findings at the time of surgery, including occult intra-abdominal metastases, and review the resulting surgical pathology in this high-risk group. We also aimed to determine the risk of complications associated with castration oophorectomy for the treatment of breast cancer. To our knowledge, no previous publications have addressed these objectives.

Materials and Methods

Vanderbilt University Medical Center's Institutional Review Board approved the protocol as a multicenter study. Minimally invasive gynecologic surgery (MIGS) fellows within the Fellowship of Minimally Invasive Gynecologist Surgery–Female Pelvic Research Network (FMIGS-FPRN) were invited to participate in this multicenter, retrospective chart review [9]. Nine academic medical centers across the country opted to participate. Participating sites reviewed the protocol and fulfilled their individual Institutional Review Board requirements.

The study population included premenopausal women with breast cancer who underwent surgical castration between January 1, 2013, and March 20, 2016, to facilitate aromatase inhibitor treatment of the cancer. These women were identified based on at least 1 office visit with a provider in the breast oncology division, a breast cancer diagnosis code, and an oophorectomy procedure code. This strategy was used to optimize the identification of patients meeting the study inclusion criteria, and to ensure inclusion of only those patients with complete data for both breast cancer diagnosis and treatment, as well as gynecologic findings and pathology results. Breast cancer diagnoses were identified using International Classification of Diseases (ICD) codes (ICD Ninth Revision: 174.4–174.9; ICD Tenth Revision: C50.00–C50.929), and oophorectomies were identified using Current Procedural Terminology codes (11000–69999). Once patients were identified, the breast oncology clinic notes were reviewed by fellows at each site to confirm study eligibility. Initial search by billing and coding data yielded 775 patient records. Additional eligibility criteria included a clinical determination of premenopausal status, active oncologic care, prescription documenting intent to start aromatase inhibitor therapy, and clinical recommendation for oophorectomy. Exclusion criteria included postmenopausal status or current use of an aromatase inhibitor as part of a separate clinical trial using multiple drugs for advanced disease. The final review of individual records yielded a cohort of 127 patients for analysis.

Patient records were reviewed for demographic and medical data, including age, ethnicity, body mass index, as well as such breast disease characteristics as cancer stage, histology, and *BRCA* status. If the patient was diagnosed with a known germline or acquired mutation, this information was collected as well, even if the significance was uncertain. Operative reports were reviewed to extract surgical data, including procedure type and operative findings, which were recorded as free text by the surgeon. Final pathological diagnoses were obtained from surgical pathology reports. Any questions regarding eligibility were resolved by consensus among reviewers from participating sites and primary investigators. Data were entered in a secure, online REDCap database with multisite access hosted at Vanderbilt University Medical Center [10].

Results

A total of 775 records across the 9 sites were reviewed, of which 127 met our final criteria for inclusion in the database for analysis. The median age of the breast cancer patients referred for oophorectomy was 46.4 years (Table 1). Eighty-five patients (69%) had stage I or II disease, 14 (11%) tested positive for *BRCA1* or *BRCA2*, and 22 (17%) had another known deleterious mutation or a mutation of uncertain significance. Before oophorectomy, 71% of the patients had already undergone chemotherapy.

There was considerable variety in the procedures performed (Table 2). Forty-three patients (35%) underwent hysterectomy at the time of bilateral salpingo-oophorectomy owing to complaints of abnormal uterine bleeding or coexisting uterine pathology. Other concomitant procedures were common as well, including ureteral stent placement, lysis of adhesions, tension-free midurethral retropubic sling, hysteroscopy, appendectomy, excision of endometriosis, ureterolysis, and endometrial biopsy. There was also notable variety in the practice of pelvic washings. Washings were sent for cytology analysis in only one-half of the cases. Eighteen patients (15%) had abnormal intra-abdominal findings noted by the surgeon in the operative report (Table 2). One patient had previously unrecognized metastatic disease on abdominal entry. Another patient had red lesions of the appendix determined to be benign on final pathology. Other notable findings included ovarian masses, uterine myomas, and adhesions. In 2 cases, the surgeon was forced to convert to laparotomy because of adhesions. Three complications were noted: 1 transfusion, 1 wound seroma and cellulitis, and 1 vaginal cuff dehiscence.

Regarding the final pathology of specimens, multiple benign conditions were noted, and a number of incidental cancers were found (Table 3). Three serous tubal intraepithelial cancers were noted, 2 in *BRCA*-negative patients. One of these patients carried a mutation in the *RAD51D* gene (c.556C > T; p.Arg186*). Multifocal endometrial epithelial neoplasia was diagnosed from a dilatation and curettage specimen obtained at the time of oophorectomy due to abnormal uterine

Table 1

Patient characteristics	
Characteristic	Value
Site, n (%) [*]	
Vanderbilt	33 (26)
Mayo Clinic Arizona	5 (4)
Mayo Clinic Florida	19 (15)
Yale New Haven Health/Bridgeport Hospital	14 (11)
Advocate General Lutheran Hospital, Illinois	4 (3)
Legacy Health, Oregon	10 (8)
Columbia University	9 (7)
Indiana University	24 (19)
University of Pittsburgh Medical Center	9 (7)
Total	127
Year of procedure, n	
2013	16
2014	31
2015	63
2016 (January–March) [†]	17
Patient characteristics	
Age, yr, median (IQR)	46.4 (41.6–49.9)
Body mass index, median (IQR)	27.8 (23.0–32.4)
Ethnicity, n (%) [*]	
White	88 (70)
Black	14 (11)
Hispanic	3 (2)
Asian	3 (2)
Middle Eastern	1 (1)
Other	2 (2)
Unknown	16 (13)
Breast cancer stage, n (%)	
I	46 (36)
II	39 (31)
III	32 (25)
IV	7 (6)
Unknown	3 (2)
<i>BRCA</i> mutation, n (%)	
I	7 (6)
II	7 (6)
Unknown	27 (21)
None	86 (68)
Breast cancer hormone receptor status, n (%)	
Estrogen receptor	123 (97.6)
Progesterone receptor	118 (93.7)
HER2 expression, n (%)	
Positive	24 (19)
Other germline or acquired mutation, n (%) [‡]	
	22 (17)

IQR = interquartile range.

^{*} Percentage total may be greater than 100 due to rounding.

[†] Incomplete year.

[‡] Including variants of uncertain significance: *ATM* gene, *MUTYH*, *BARD1* [c.1977A > G], *BRCA1* (S324R(1089A > C)), *RAD50* p.V315L (c.943G > T), *STK11* [c.1211C > T], *PTEN* [c.-1196_-1185del12], *PALB2* [c.2106A > G (p.Ile702Met)], *CHEK2*, *ATM* p.V2424G, *BRIP1*, *TP53*, *Li-Fraumeni*, *BRCA2* [c.-14T > C], *PTEN*, Lynch syndrome, *MUTYH* carrier, *ATM* c.7010G > A (p.C2337Y), *RAD51D* c.556C > T (p.Arg186*).

Table 2

Operative findings	
Variable	Value
Procedure performed, n*	
TLH BSO	34
LSC BSO (LSO or RSO)	107
Abdominal BSO	1
TAH BSO	4
TVH BSO	3
LAVH BSO	1
Other [†]	30
Conversion to laparotomy	2 (due to adhesions)
Washings, n (%)	
Pelvic washings sent to cytology	64 (50)
Operative findings, n (%)	
Abnormal [‡]	18 (15)
Complications, n	
Transfusion	1
Intraoperative injury (enterotomy, cystotomy)	0
Readmission within 7 days due to postoperative complications	0
Other (wound seroma and cellulitis, vaginal cuff dehiscence)	2
BSO = bilateral salpingo-oophorectomy; LAVH = laparoscopic assisted vaginal hysterectomy; LSC = laparoscopic; LSO = left salpingo-oophorectomy; RSO = right salpingo-oophorectomy; TAH = total abdominal hysterectomy; TLH = total laparoscopic hysterectomy; TVH = total vaginal hysterectomy.	
* Patients could have more than 1 procedure.	
[†] RA-BSO (2), dilatation and curettage (7), ureteral stent placement, SILS (2), RA-SILS BSO (2), LOA, (12) RA-TLH BSO, tension-free midurethral retro-pubic sling, hysteroscopy, appendectomy, excision of endometriosis (2), ureterolysis, endometrial biopsy, RA-SCH BSO.	
[‡] Abnormal findings grouped by organ (n if multiple): adhesions (4); ovary: simple cyst, endometrioma; ovarian cyst, likely cystadenoma, cystic mass, multiple ovarian cysts, cystadenofibroma; liver: white lesions; appendix: red lesions; peritoneum: endometriosis (3), cyst; uterus: 16-cm pedunculated fibroid; fallopian tube: paratubal cysts, excrescences.	

bleeding and history of tamoxifen use. She later underwent hysterectomy, and the specimen was notable for focal residual intraepithelial neoplasia.

Evidence of previously unrecognized advanced disease was also noted pathologically in 1 pelvic washing specimen and 2 ovarian specimens with metastatic disease. Another 9 patients had benign ovarian pathology, most commonly serous cystadenoma. Among uterine specimens, 5 were abnormal with 1 case of grade 2 endometrial adenocarcinoma, endometrioid type. The patient diagnosed with endometrial cancer had abnormal bleeding at the time of her presentation for oophorectomy, and an office biopsy led to the diagnosis of endometrial cancer. Her *BRCA* status was unknown. The most common benign uterine condition was leiomyoma.

During the study period from 2013 to 2015, the number of patients meeting our study criteria and seen by gynecologic surgeons in the FPRN for oophorectomy increased by nearly 400% (Table 1).

Discussion

Our study noted a wide variation in surgical approach for premenopausal women undergoing oophorectomy to facilitate adjuvant hormonal therapy. Also observed was a wide variety of pathological diagnoses, including benign, precancerous, and malignant conditions, found at the time of oophorectomy. Ovarian pathology included metastatic tumors, serous cystadenomas, endometriomas, and Brenner tumors. An unexpectedly high number of other malignant conditions were found as well. Three serous tubal intraepithelial cancers were found, 2 in *BRCA*-negative patients. This rate is higher than rates previously published for the general population [11]. Among the uterine specimens, 1 endometrial adenocarcinoma and 1 multifocal endometrial intraepithelial neoplasia were noted.

Unfortunately, premenopausal breast cancer is a prevalent condition in the United States, and many gynecologists will see these patients in the office setting. The number of premenopausal breast cancer patients seen for surgical castration to facilitate aromatase inhibitor therapy by gynecologists in the participating FPRN sites increased by nearly 400% from 2013 to 2015. This trend likely reflects the change in breast oncology practice in response to the SOFT trial data and indicates possibly greater numbers of future referrals for oophorectomy in this patient population.

Limitations of this study include the retrospective design based on billing data to identify the study population and chart review to capture data, which carry a risk of misclassification bias. The initial identification of each patient is dependent on institutional methodology and billing and coding systems, which vary across centers. Thus, the data retrieval method for chart review in our starting population could not be exactly replicated at each site. To reduce this bias as much as possible, we cast a wide net to identify the starting population, and then manually reviewed each record for final inclusion. In addition, these data were collected from large medical centers, likely reflecting a referral population with higher-risk disease, and thus the data may overrepresent the true prevalence of the conditions noted. A strength of this study is its large population collected from multiple centers across the United States. To our knowledge, this is the first study describing operative practices and surgical pathology for this indication in this particular patient group.

Although our study group contained a number of women with *BRCA* mutations, the recommended surgical management of which is well documented [12], the majority of the patients were *BRCA*-negative. Many carried mutations known to be associated with an increased risk of malignancy, as well as mutations of uncertain significance that carry as-yet unclear risks of synchronous cancers. Furthermore, women who develop breast cancer before menopause are at baseline a high-risk disease group that may have occult metastases [13].

Our data suggest that gynecologists serving this population should have a high index of suspicion for other

Table 3

Surgical specimen findings		
Specimens submitted	Abnormal findings*	Description of findings
Pelvic washings (64)	Abnormal 1	Metastatic adenocarcinoma
Ovarian pathology (127)	Abnormal 13 (10%)	Metastatic breast carcinoma with lymphatic space involvement, metastatic adenocarcinoma of both ovaries, likely breast
	Neoplastic 2	
Tubal pathology (127)	Benign 11	Serous cystadenoma (6), stromal thecosis, PCOS, endometriotic cysts, benign serous cyst, Brenner tumor, endometriosis, serous cystadenofibroma
	Abnormal 8 (6%)	
Uterine pathology (46)	Neoplastic 3	Focal serous tubal intraepithelial carcinoma (3)
	Benign	
Other pathology (24) [†]	Abnormal 5 (11%)	Hydatid cysts, paratubal cysts (3), chronic salpingitis, endometriosis
	Neoplastic 1	
	Benign 4	Endometrial adenocarcinoma, endometrioid type grade 2
	Abnormal 3 (13%)	
	Neoplastic 1	Leiomyoma (4), chronic cervicitis (2), endometrial polyp, endometriosis, complex hyperplasia without atypia, adenomyosis
	Benign 2	
		Multifocal EIN
		Endometriosis (2)

EIN = endometrial intraepithelial neoplasia; PCOS = polycystic ovary syndrome.
 * Some patients had multiple diagnoses.
 † Peritoneal biopsy, endometrial curettage, etc.

malignancies or occult metastatic disease. Good clinical practice should include a thorough abdominal survey at the time of surgery with strong consideration of pelvic washings. Consideration also should be given to serial sectioning of fallopian tube and ovary specimens with microscopic examination, even in *BRCA*-negative patients. In addition, given the cases of endometrial hyperplasia and neoplasia noted in our population, a careful history of abnormal bleeding should be obtained with a low threshold for endometrial sampling.

Conclusion

Premenopausal breast cancer patients may be a growing population seen by gynecologists as more are recommended to undergo surgical oophorectomy to facilitate adjuvant hormonal therapy. Our data suggest that current surgical practice in this population is variable. The data also show that it is not uncommon for these patients to have other cancers, precancerous conditions, and previously unrecognized metastatic diseases. Gynecologists serving this patient population may consider careful abdominal surveys, pelvic washings, endometrial sampling, and serial sectioning of ovarian and fallopian tube specimens for a thorough evaluation.

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