Oophorectomy in Breast Cancer—Controversies and Current Status

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Abstract The role of oophorectomy in the treatment of breast cancer is known for over 100 years. Ovarian ablation has a relatively large positive effect on both disease-free survival (DFS) and overall survival (OS) in premenopausal women when compared to no adjuvant treatment. Today the standard of care in adjuvant therapy of endocrine responsive tumors in premenopausal women is tamoxifen with or without chemotherapy. The role of oophorectomy /ovarian ablation in current surgical practice is discussed and important issues highlighted in the article.

Keywords Oophorectomy · Ovarian ablation · Breast cancer

The role of oophorectomy in the treatment of breast cancer is known for over 100 years. Thomas William Nunn was the first to report a relationship between ovarian function and breast cancer when he described regression of breast cancer in a woman 6 months after she attained menopause. Albert Schinzinger, a German surgeon was the first to propose oophorectomy as a treatment for breast cancer but he never performed the surgery himself. George Thomas Beatson was the first person to perform a bilateral oophorectomy on a woman with breast cancer in 1895. He reported on three patients in the *Lancet* in 1896. A subsequent report indicated that one patient survived 4 years after the surgery. The procedure never became popular because of the associated high morbidity in the early 20th century. In the 1950s, Charles Huggins and Thomas Dao popularized oophorectomy

along with adrenalectomy, and brought them back to the mainstream of breast cancer therapy [1].

Oophorectomy was not tested in large randomized trials until the middle of the 20th century. The few small randomized trials that were carried out showed inconsistent results. The first large body of evidence in favour of oophorectomy was the first overview published by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in 1984. This and the subsequent overview published in 2005 showed that ovarian ablation had a relatively large positive effect on both disease-free survival (DFS) and overall survival (OS) in premenopausal women when compared to no adjuvant treatment [2, 3].

Several others developments took place in the treatment of breast cancer that affected the use of oophorectomy. These included alternate methods for ovarian ablation/suppression, the detection of estrogen receptors, and the use of chemotherapy and tamoxifen for adjuvant treatment of breast cancer.

Today the standard of care in adjuvant therapy of endocrine responsive tumors in premenopausal women is tamoxifen with or without chemotherapy. The question which needs to be answered is what is the role, if any, of oophorectomy in the current management of breast cancer?

The first fact that needs to be highlighted is the target population. Premenopausal patients with ER/PR positive tumors are the ones who can be selected for oophorectomy. The commonest age for breast cancer in India is between 45 and 50 years, a decade younger than in the West. We are thus more likely to see premenopausal patients. ER positivity is related to age, being more frequent as the age advances. Thus we may see less endocrine responsive tumors. It is very important to define the target population based on the above factors.

The next fact that needs to be highlighted is that ovarian suppression with Luteinizing Hormone Releasing Hormone (LHRH) analogues have been shown to be equally effective as

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oophorectomy. The advantages of ovarian suppression include its reversible effect and the lack of operative morbidity. The disadvantages include its side effects and its cost, the latter being very important in India. For the remaining discussion we will assume that the effects of oophorectomy and ovarian suppression are similar.

The first question to be answered is the efficacy of ovarian ablation/suppression versus tamoxifen. There is only one randomized trial of 320 patients with node positive and hormone receptor positive or receptor status unknown tumors comparing goserelin with tamoxifen. No differences in time to first recurrence or overall survival were observed between treatment groups but the number of patients was too small to formally exclude a potentially clinically relevant difference in survival [4].

Although not designed for this objective, indirect evidence from the ZIPP (Zoladex in Premenopausal Patients) trial also shows similar results. At a median follow-up of 12.3 years, goserelin reduced the risk of first event by 32% in the absence of tamoxifen, and tamoxifen reduced the risk by 27% in the absence of goserelin [5].

From the small body of evidence that exists, it appears tamoxifen and ovarian ablation/suppression have a similar effect. However, it is relevant that the information comes from small numbers or from trials not specifically designed to test this. Also, patients with unknown receptor status have been included which could dilute the results.

Can the combination of tamoxifen and ovarian suppression be additive? Individual patient data (11,906 premenopausal women with early breast cancer) from 16 published trials were analyzed, including women with tumours positive for ER, PR or both. The main endpoints were recurrence and death after recurrence. In a subset of 1,013 women comparing tamoxifen with or without LHRH agonist, no significant difference was found for the addition of LHRH agonist to tamoxifen for recurrence or death after recurrence [6].

The next question to be answered is the interaction between ovarian ablation/ suppression and adjuvant chemotherapy. Chemotherapy induces amenorrhea in premenopausal women and it is believed that the beneficial effect of chemotherapy is because of it inducing ovarian failure. This belief is strengthened by the fact that women who achieve amenorrhea have a better outcome than those who do not [7].

A meta-analysis of 7 randomized trials comparing CMF (Cyclophosphamide, Methotrexate, 5 Fluorouracil) with ovarian ablation/suppression did not show a significant difference in either DFS or OS. It must be remembered that CMF is not considered standard of care in current practice. Current adjuvant chemotherapy often includes anthracyclines and taxanes. There is no data to suggest equivalence or superiority/inferiority of ovarian ablation/suppression over current adjuvant chemotherapy.

Is there any advantage of adding ovarian ablation/suppression to the current standard practice of chemotherapy and tamoxifen? A patient-level meta-analysis by Cuzick et al [6], based on data from the ZIPP trials examined this question. The meta-analysis ($n=365$) found no significant difference for recurrence and death after recurrence. In the same publication, the addition of ovarian ablation/suppression to any systemic therapy, defined as tamoxifen, chemotherapy, or the combination of both was analyzed (407 patients). The addition of ovarian ablation/suppression to any systemic therapy was associated with a significant benefit in terms of recurrence and death after recurrence.

Premenopausal, node positive, ER positive patients ($n=1503$) were randomly assigned to receive 6 cycles of FAC alone, or FAC followed by goserelin for 5 years (FAC-Z) or FAC followed by 5 years of monthly goserelin and daily tamoxifen (FAC-ZT). The primary end points were time to recurrence (TTR), disease-free survival (DFS), and overall survival (OS). With a median follow-up of 9.6 years, the addition of tamoxifen to CAF-Z improved TTR and DFS but not OS. There was no overall advantage for addition of goserelin to FAC. What is more interesting was an unplanned retrospective analysis by age (more or less than 40 years) which showed an advantage of adding goserelin to women younger than 40 years in terms of DFS [9].

The effect of chemotherapy on ovarian function is related to age, with younger women tending to have a lower incidence of permanent ovarian failure. It would thus be logical for these patients to benefit from additional ovarian suppression.

Current Indications of Ovarian Ablation/Suppression

The practice guidelines developed by Cancer Care Ontario and endorsed by the American Society of Clinical Oncology state that in premenopausal women with HR-positive breast cancer who cannot tolerate or who refuse chemotherapy, ovarian ablation/suppression remains a viable treatment option. They do not recommend the addition of ovarian ablation to chemotherapy and tamoxifen due to lack of evidence [8, 10].

In India where cost of treatment, compliance to treatment and follow up are major issues, ovarian ablation may be good alternative to adjuvant systemic therapy. Considering cost factors, a laparoscopic oophorectomy may be the procedure of choice in India.

We need to develop better methods of assessing ovarian function after chemotherapy. If we can accurately identify women with significant ovarian function or reserve after chemotherapy, we may possibly have a subset of patients who may benefit from additional ovarian ablation.

Take Home Message

- The target population needs to be correctly identified by assessing hormone receptors.
- Oophorectomy may be a good alternative in a patient who cannot afford or tolerate adjuvant systemic therapy.
- The evidence for or against ovarian ablation/suppression is based on trials which suffer from small numbers and the use of modern day adjuvant chemotherapy.
- Identification of women with residual ovarian function after chemotherapy may identify a potential subset which may benefit from additional ovarian ablation.
- In India, laparoscopic oophorectomy may be a better alternative than ovarian suppression with LHRH analogues.

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