Epworth Breast Service

Breast Cancer Update 2014

We genuinely strive to continually improve the level of care we provide to our patients with breast problems, with the ongoing goal of providing our patients with the best breast care possible. We aim to support and empower our patients to navigate the breast cancer journey and a vital component of our role is to educate and inform ourselves, and update our patients and their general practitioners on a regular ongoing basis.

The past few months has seen the presentation of a number of potentially "practice changing" studies and the publication of several new practice guidelines likely to influence the clinical management of breast cancer. The results of the premenopausal breast cancer studies are of particular interest to us, as we treat many younger breast cancer patients and personally contributed patients to the three international trials outlined, which have provided some answers to important clinical questions in this age group.

Miss Jane O'Brien
MBBS FRACS
Specialist Breast and
Oncoplastic Surgeon
Epworth Breast Service

ASCO Guidelines Recommend Tamoxifen for 10 Years for Hormone-Sensitive Breast Cancer

Tamoxifen is now recommended for 10 years instead of just 5 years for women with hormone-receptor-positive breast cancer, according to new guidelines from the American Society of Clinical Oncology (ASCO) released in May 2014 based on recent studies which have shown improved survival with extended tamoxifen, as well as reduced risk for recurrence and contralateral breast cancer.

ASCO, the world's leading professional organization representing physicians who care for people with cancer, recently issued an update to it's clinical practice guideline on the use of adjuvant endocrine therapy for women with hormone receptor positive breast cancer, reflecting new data on the duration of tamoxifen treatment. In the two largest randomized studies that had the longest follow-up (ATLAS and ATTOM) women who took tamoxifen for 10 years had a breast cancer survival advantage, as well as lower risks of breast cancer recurrence and contralateral breast cancer, compared to those who took tamoxifen for five years.

Hormone receptor-positive (HR+) breast cancer is the most common type of breast cancer worldwide. About 60 percent to 75 percent of women with breast cancer have oestrogen receptor-positive (ER+) breast cancer and 65 percent of these cancers are also progesterone receptor-positive (PgR+). Adjuvant endocrine therapy is highly effective and appropriate for nearly all women with ER and/or PgR positive tumors.

"Tamoxifen taken for five years has been the standard adjuvant endocrine treatment for decades, but we now have evidence to recommend up to 10 years of tamoxifen for women with hormone receptor-positive breast cancer. Postmenopausal women also have the option of taking an aromatase inhibitor as an alternative to tamoxifen or in sequence after tamoxifen. Aromatase inhibitors are not recommended for premenopausal women."

Key ASCO guideline recommendations:

- Women diagnosed with hormone receptor-positive breast cancer who are pre-/peri- menopausal should be offered adjuvant endocrine therapy with tamoxifen for 5 years, after which they should receive additional therapy based on menopausal status. If premenopausal, they should be offered continued tamoxifen for a total duration of 10 years. If postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or an aromatase inhibitor (AI) for a total duration of up to 10 years of adjuvant endocrine therapy.
- Women diagnosed with hormone receptor-positive breast cancer who are postmenopausal should be offered adjuvant endocrine therapy with one of the following options: tamoxifen for 10 years; an AI for 5 years; tamoxifen for 5 years, then switching to an AI for up to 5 years; or tamoxifen for 2-3 years and switching to an AI for up to 5 years.
- Women who are postmenopausal and are intolerant of either tamoxifen or an AI should be offered the alternative type of adjuvant endocrine therapy. If women have received an AI, but discontinued treatment at less than 5 years, they may be offered tamoxifen for a total of 5 years. If women have received tamoxifen for 2-3 years, they should be offered an AI for up to 5 years, for a total duration of up to 7-8 years of adjuvant endocrine therapy.

The guideline also discusses issues clinicians face in communicating with women about taking adjuvant endocrine therapy for extended periods of time. It is important for clinicians and patients to discuss the trade-offs between potential risks of side effects and potential benefits of taking adjuvant endocrine therapy for up to 10 years, Many women taking adjuvant tamoxifen experience side effects, and these appear to persist with longer duration. However, the extended trials did not find any new or unexpected side effects.

The guideline is available at www.asco.org/guidelines/endocrinebreast and information explaining what the recommendations mean for patients is available at www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/hormonal-therapy-hormone-receptor-positive-breast-cancer

TAKE HOME MESSAGE: Ten years of endocrine therapy should be considered in women with hormone receptor positive breast cancer instead of the previously recommended five years.

Level 7, 32 Erin St, Richmond. 3121
T: 9421 4218 F: 9421 5148
www.melbournebreastcancersurgery.com.au

Updated American College of Obstetricians and Gynecologists (ACOG) Committee Opinion on Tamoxifen and Uterine Cancer Supports extended Tamoxifen

The American College of Obstetricians and Gynecologists (ACOG) published an updated Committee Opinion on Tamoxifen and Uterine Cancer in the June 2014 issue of Obstetrics & Gynecology, supporting the safety of 10 years of tamoxifen.

Tamoxifen, as a selective oestrogen receptor modulator, although primarily antioestrogenic, also has mild oestrogenic activity and as a consequence, it appears to result in a 2 to 3 fold increased relative risk of developing endometrial cancer, which is dose and time dependent, however studies suggest that the small risk of developing endometrial cancer is outweighed by the significant survival benefit provided by tamoxifen therapy for women with breast cancer.

Although several approaches, including transvaginal ultrasonography and endometrial biopsy, have been used to screen for endometrial proliferation or endometrial cancer in asymptomatic women prescribed tamoxifen, none have proven effective according to the committee. Such surveillance may lead to more invasive diagnostic procedures and is therefore not recommended. However prescreening women before they initiate tamoxifen therapy may identify patients with benign polyps, who are at higher risk for atypical hyperplasia. The committee noted that if a woman taking tamoxifen develops atypical endometrial hyperplasia, the clinician should manage that condition and reassess the use of tamoxifen.

On the basis of all of the data, the committee recommended the following:

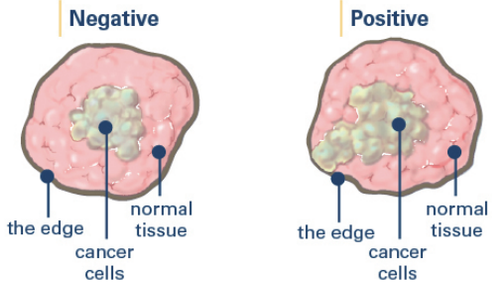
- Tamoxifen use may be extended to 10 years on the basis of new data demonstrating additional benefits.
- Clinicians should inform women taking tamoxifen about the risks for endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas.
- Clinicians should investigate any abnormal vaginal bleeding, bloody vaginal discharge, staining, or spotting.
- Clinicians should closely monitor postmenopausal women taking tamoxifen for symptoms of endometrial hyperplasia or cancer.
- Although several approaches , including transvaginal ultrasonography and endometrial biopsy, have been used to screen for endometrial proliferation or endometrial cancer in asymptomatic women prescribed tamoxifen, none have proven effective. Such surveillance may lead to more invasive diagnostic procedures and is therefore not recommended.
- No additional monitoring is needed for premenopausal women taking tamoxifen, as there is no evidence to show they are at increased risk for uterine cancer.

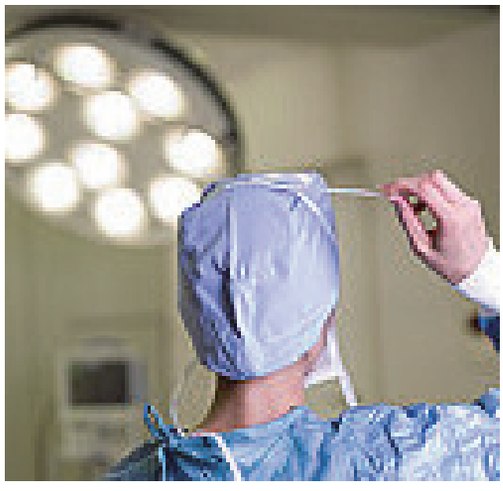
TAKE HOME MESSAGE: In the absence of symptoms, routine screening for uterine cancer in women receiving tamoxifen is not indicated.

New Guideline Addresses Acceptable Breast Cancer Margins in Breast Conserving Surgery

A new guideline on pathological margins in breast cancer therapy establishes "no ink on tumour" be the standard for an adequate margin in patients with invasive cancer undergoing breast conserving surgery/lumpectomy.

The American Society of Surgical Oncology and the American Society for Radiation Oncology guideline is based on a meta-analysis and review of 33 research studies published between 1965 and 2013.The new approach is expected to reduce re-excision rates, improve cosmetic outcomes and potentially cut health care costs. Currently, about one in four breast cancer patients in the United States undergoes re-excision after lumpectomy, and nearly half of these procedures are performed with the rationale of obtaining wider margins in women whose tumour cells do not touch the inked margin.





The American Society of Clinical Oncology and the American Society of Breast Diseases have also endorsed the recommendations, and one of the strengths of the new guideline is that professional organizations representing surgeons, radiation oncologists, pathologists and medical oncologists all support the recommendations,

Prior to these guidelines, there was no consensus on the optimal width of negative margins in breast-conserving surgery for invasive breast cancer. Many treatment teams had rules that all margins had to be 2 mm, 5 mm, or even 1 cm, in the belief that this would decrease local recurrence. The guideline says such rules are inappropriate and promote unnecessary surgery. This doesn't mean that in selected patients a margin wider than no ink on tumour will not be beneficial, but what it does mean, is that wider margins are not the standard. The panel's review found that these recommendations can be applied to a patient of any age and for women with more aggressive disease, including those with triple-negative breast cancer.

The guidelines include several recommendations about margins after lumpectomy to remove early-stage breast cancer, including:

- If there is ink on tumour, the risk of recurrence in the same breast is doubled.
- Clear margins offer the lowest risk of recurrence in the same breast; wider clear margins don't reduce this risk any further.

- Wider margin widths do not significantly lower the risk of local recurrence, regardless of a woman's age or the biologic subtype. Women younger than 40 who are diagnosed with early-stage breast cancer have a higher risk of recurrence in the same breast after lumpectomy. There is no evidence that a wider margin reduces these risks and a clear margin width is the same for a cancer that is hormone-receptor-positive or hormone-receptor-negative.
- Adjuvant therapies, such as hormonal therapy, radiation therapy and chemotherapy, reduce the risk of recurrence in the same breast, however, even if a woman doesn't have adjuvant treatments, there is no evidence that the clear margins need to be wider than no ink on tumour.
- Choice of whole-breast radiation delivery technique, fractionation and boost dose should not be dependent on the margin width.
- Positive margins, defined as ink on tumour, are associated with at least a twofold increase in local recurrence in the breast, and this risk is not nullified by delivery of a boost, delivery of systemic therapy or favourable biology, and further surgery is recommended.

The key is that like any guideline, it simply provides a framework, and clinical decision making must still be individualized for each patient, to account for the patient's risk for breast cancer relapse and how much a re-excision will decrease that risk. Some patients with close margins may benefit from additional surgery, and each case should be individually evaluated in a multidisciplinary fashion, considering all important clinical, pathologic, and treatment variables. The routine recommendation however for margin re-excision for all narrow—1 or 2 mm—margin widths is no longer felt to be justified. The current guidelines apply to patients with invasive breast cancer who subsequently received whole-breast radiation therapy. The results cannot be extrapolated for patients receiving neoadjuvant chemotherapy or accelerated partial-breast irradiation or for patients diagnosed with ductal carcinoma in situ (DCIS) only.

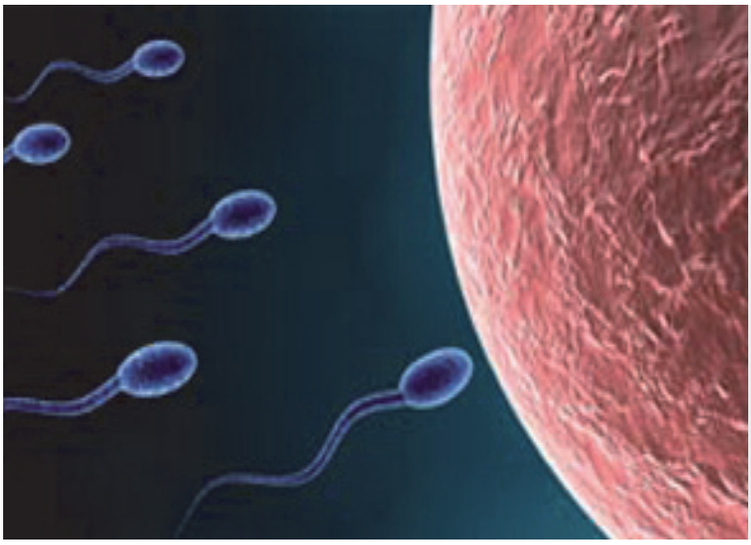
TAKE HOME MESSAGE: Margin re-excision to achieve lumpectomy margin widths wider than "no ink on tumour" is no longer routinely indicated.

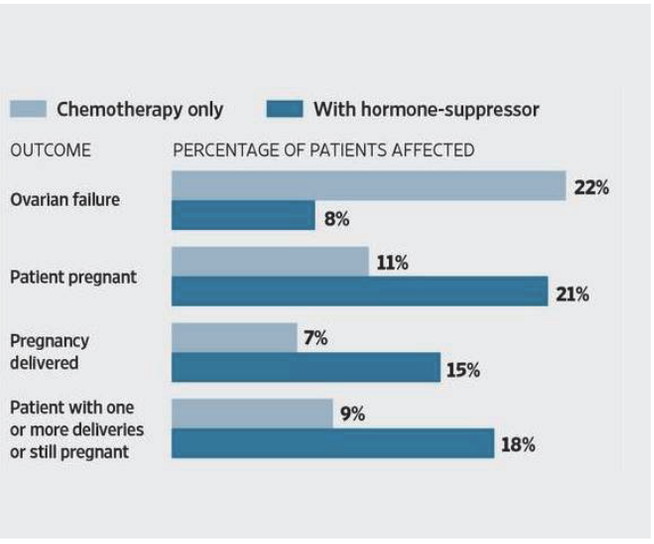
Hormone Suppressing Drug Preserves Fertility During Breast Cancer Chemotherapy

Early menopause and loss of fertility can be devastating effects of chemotherapy for young women with breast cancer, however the use of the hormone-suppressing drug goserelin (Zoladex, AstraZeneca) during chemotherapy for breast cancer minimizes both risks, according to a study presented at the annual ASCO Meeting in May 2014. A global randomised clinical trial has shown inducing temporary 'hibernation' of the ovaries of premenopausal women with hormone-receptor negative breast cancer, through a monthly injection of goserelin, a drug that disrupts the body's hormonal feedback systems causing temporary menopause, helps prevent chemotherapy-induced menopause and preserve fertility.

Premature ovarian failure is a common side effect of the standard chemotherapy used for breast cancer treatment, with a woman's personal risk of early menopause depending on the type, dose and duration of chemotherapy she receives, as well as her age and a number of other factors.

The POEMS study, (Prevention of Early Menopause Study) found that temporarily shutting down the ovaries increased the likelihood they will return to function after the conclusion of treatment - something that has been pursued, with inconclusive results, for more than a decade. To try to preserve fertility, the researchers looked at using Zoladex, a drug that temporarily shuts down ovarian function. It is thought that this protects the ovarian follicles from chemotherapy damage. Premenopausal women with hormone-receptor negative breast cancer were randomly assigned to receive standard chemotherapy with or without goserelin every four weeks. All 218 patients underwent chemotherapy and half also received monthly injections of goserelin, starting 1 week before the first dose of chemotherapy.





The trial showed that pre-menopausal women with hormone-receptor negative breast cancer who received goserelin during chemotherapy had a 64 per cent reduction in their chance of early menopause, and were almost twice as likely to have had a baby after the end of their cancer treatment, compared to women who didn't received the injections.

Two years after starting chemotherapy, 8% of women who took goserelin experienced ovarian failure compared with 22% of women who only received chemotherapy. During this time, 21% women who took goserelin became pregnant compared with 11% who only received chemotherapy. These pregnancies resulted in 15% women in the goserelin group delivering at least one baby versus 7% in the chemotherapy group. A limitation of the study was missing endpoint data for 38% of participants. According to the researchers, goserelin did not increase the risk of miscarriage or pregnancy termination.

The POEMS results were of particular interest to us locally as we personally recruited and contributed patients to the study. Melbourne medical oncologist Kelly Phillips was the Australasian and European Study Chair of the POEMS trial and more than 20% of the women who participated in the study came from Australasia.

TAKE HOME MESSAGE: In pre-menopausal women with hormone-receptor negative breast cancer, temporary ovarian function suppression during chemotherapy may help prevent chemotherapy-induced menopause, and preserve fertility.

New Treatment Option for Young Women with Hormone-Sensitive Breast Cancer

The results of two international clinical trials show that the aromatase inhibitor(AI), exemestane, is more effective than tamoxifen in preventing breast cancer recurrence in young women with hormone sensitive early breast cancer who also receive ovarian function suppression.

The combined results of TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial) were announced at a plenary session at the annual meeting of ASCO in May 2014, a meeting attended by 33,000 delegates, and were published simultaneously online in the New England Journal of Medicine. Premenopausal women with hormone-sensitive, early-stage breast cancer demonstrated a significantly reduced risk of recurrence when they received the aromatase inhibitor exemestane compared with tamoxifen, after ovarian function suppression (OFS),

When treating premenopausal women with hormone receptor positive (HR+) breast cancer, the optimal adjuvant endocrine therapy is still uncertain. Just under 25 percent of women with breast cancer are diagnosed under the age of 50, and approximately eight out of 10 of these cancers are hormone-responsive. For postmenopausal women, clinical trials over the past 15 years have shown adjuvant aromatase inhibitors for 5 years to be a more effective treatment strategy than 5 years of tamoxifen in many postmenopausal women. This treatment was not available to premenopausal women, because AIs require the low oestrogen levels that occur after menopause to be effective, and these levels can only be achieved in young women with OFS.

A joint analysis of the two trials involving a total of 4690 premenopausal women with HR+ breast cancer demonstrated that adjuvant use of the aromatase inhibitor (AI), exemestane, reduced the relative risk of developing subsequent invasive cancer by 28% compared with tamoxifen, when both agents were combined with ovarian function suppression (OFS). The exemestane + OFS treatment arm also showed a relative reduction in the risk of breast cancer recurrence of 34%. The trials demonstrate that an aromatase inhibitor, previously recommended only for postmenopausal women, is also effective for premenopausal women when combined with ovarian function suppression.

The overall results were very similar to those in the postmenopausal setting, with the magnitude of benefit derived from an AI (plus OFS) similar to the benefit seen in the ATAC trial, comparing tamoxifen with an the AI anastrozole (Arimidex), which led to a shift in practice in postmenopausal women. These results are likely to change practice, although not necessarily by establishing a new standard of care, but by providing another option. This result does not mean that we need to give all premenopausal women with HR+ positive disease the combination. We need to figure out who really needs this, because an AI plus ovarian suppression will cause more toxicity than tamoxifen alone. There are some women for whom tamoxifen alone is fine, just as there are some women in the postmenopausal age for whom tamoxifen alone is fine.

Also of note, many patients in these trials did not receive chemotherapy and yet had an excellent prognosis with endocrine therapy alone. This finding emphasizes that not all premenopausal women require chemotherapy.

The remaining important question is whether ovarian suppression adds much to tamoxifen, as it is not yet clear whether the ovarian suppression is adding anything to tamoxifen alone. To make sure that shutting off the ovaries actually added to the benefit of tamoxifen -as suspected, the SOFT trial also included a tamoxifen without ovarian suppression arm, to mimic the current standard of care. The full results of SOFT will be presented in December at the San Antonio Breast Cancer Symposium in December 2014.

These two trials were also of great interest to us personally, as we recruited and contributed patients to both studies. Worldwide 2,672 women were enrolled in TEXT, including 249 women from Australasia and 3,066 women were enrolled in SOFT including 240 women were from Australasia. Melbourne medical oncologist Prue Francis chaired the International Steering Committee responsible for TEXT and SOFT, and is the senior author of the publication of the results in the New England Journal of Medicine.

TAKE HOME MESSAGE: An aromatase inhibitor, previously recommended only for postmenopausal women, is also effective for premenopausal women when combined with ovarian function suppression, and presents a new treatment option for premenopausal women with hormone-responsive breast cancer.

Epworth Breast Service Specialist Breast and Oncoplastic Surgeons

Fewer than 8% of Australian surgeons are female, and the Epworth Breast Service is therefore very fortunate and proud to be able to offer our breast patients the expertise of two highly trained and extremely experienced female specialist breast and oncoplastic surgeons, both of whom have extensive international training and experience.

Miss Jane O'Brien
MBBS 1985
University of Melbourne
FRACS 1995

Miss Melanie Walker
MBBS 1994
Monash University
FRACS 2002

Copies of this update may be downloaded from www.melbournebreastcancersurgery.com.au

Epworth Breast Service
Comprehensive Multidisciplinary Breast Cancer Management
Level 7, 32 Erin St, Richmond. 3121
T: 9421 4218 F: 9421 5148
www.melbournebreastcancersurgery.com.au