

Chapter 9
Systemic Adjuvant Therapy
of Breast Cancer

During the last twenty years, the incidence of breast cancer has increased in Europe and in the USA. However, a parallel increase has not been noted in mortality due to breast cancer. In fact, since 1994 there has been a 1% to 2% reduction in mortality in the USA, Canada, Sweden, France, and the UK. This is for two main reasons. First, by the development of early diagnosis, based on radiological and clinical detection and secondly, the use of systemic adjuvant therapy.

The rationale for the use of systemic adjuvant treatment following loco-regional therapy of breast cancer is :

1. The relation between the tumor volume and the risk of metastatic dissemination: this risk is estimated at over 50% for a volume of more than 40 mm;
2. The efficacy of adjuvant therapy, chemotherapy or hormone therapy, is tumor volume dependent, : the greater the volume, the higher the risk of acquiring the drug-resistance phenotype; and
3. Progress in loco-regional therapy does not seem to enhance survival, since it has failed to prevent metastatic dissemination.

A better appraisal of prognostic parameters currently allows a more accurate definition of the groups of patients in whom systemic adjuvant therapy is relevant. Moreover, some of these factors e.g. axillary node status, estrogen, and progesterone receptors, nuclear grade, tumor size and age are decisive for the choice between adjuvant hormonal therapy and chemotherapy.

Before addressing specific adjuvant therapies, it is important to address the necessity, of any adjuvant systemic therapy. Two groups who do not need adjuvant therapy may be suggested. Those who will not benefit, because their prognosis is so favorable and those for whom adjuvant therapy is ineffective.

It appears from the present data that women with node negative breast cancer <1 cm in diameter or 1-2 cm in diameter and have histologic grade 1 tumors (T1a,b N0 or T1c grade 1 N0) have the same survival likelihood as age-matched women without breast cancer. So, adjuvant systemic therapy may not be indicated. The second group, where adjuvant systemic therapy is ineffective includes giving hormonal therapy for women whose tumors lack hormone receptors, trastuzumab for women with low levels of HER-2 expression, and giving cytotoxic chemotherapy for very old women, as they appear to receive only toxicity without benefit.

I. ADJUVANT ENDOCRINE THERAPY

I.1. Selective Estrogen Receptor Modulators [SERMs]

Tamoxifen is the first SERM to be tested. The EBCTCG data clearly demonstrate that 5 years of daily tamoxifen reduces the risk of recurrent breast cancer by 47% in receptors positive women. This reduction is also durable. The benefit of 5 years of tamoxifen appears greater than with 2 years, which is greater than that seen with one year of therapy. But limited data exists on the value of greater duration. A very large international clinical trial of duration (ATLAS trial) including 15V 252 is underway to resolve this issue. Benefits in addition to prevention of metastatic breast cancer include improved local control and prevention of contralateral breast cancer in individuals with a hormone receptor-positive primary tumor.

The detrimental aspects of tamoxifen include menopausal symptoms, endometrial cancer, and thromboemboli. The latter two are seen only (are you sure for thrombo-embolism?) in postmenopausal

women. Very rarely, there may be an accelerated progression of certain types of cataracts, but this is uncertain. However, the benefit of giving tamoxifen greatly outweighs the hazards. The benefit of reduction of contralateral breast cancer is alone able to counterbalance the increased risk of endometrial cancer, quite aside from the other benefits of systemic adjuvant effects.

It is now very clear and conclusive that the benefit of tamoxifen is only for those with hormone receptor-positive tumors, even those with low levels of receptor expression.

A further area of controversy concerns the use of adjuvant tamoxifen in women with tumors overexpressing Her-2; an overexpression to Her-2 is associated in the lab with tamoxifen resistance. However, and based on existing clinical data, it appears appropriate to treat patients only based on hormone-receptor status and not to deny tamoxifen when Her-2 is overexpressed.

The search continues for tailored SERMs that retain only desirable effects of tamoxifen. Other SERMs such as raloxifene have not been tested sufficiently, while the so-called SERM-3 agents are nearing clinical testing. So, at present, tamoxifen is the only SERM used outside adjuvant clinical trials and the most potent adjuvant available for the receptor-positive patient.

I.2. Anti-estrogens

The finding that both steroidal aromatase inhibitors e.g. exemestane (Aromasin)[®], and non steroidal aromatase inhibitors e.g. letrozole (Femara)[®], and anastrozole (Arimidex)[®], can provide major response in the advanced and metastatic disease has suggested about their role in adjuvant therapy. Results of recent clinical trials show a benefit in term of disease free survival of antiaromatase over tamoxifen. Others trials are now ongoing to answer whether the use of sequential administration of tamoxifen and antiaromatases either during five years of each treatment, or 2.5 years of each increases the quality of the results. Long term tolerance of antiaromatases is mainly marked by the risk of major osteoporosis.

Fulvestrant is a pure anti-oestrogen that reduce markers of hormone sensitivity and proliferation of breast cancer. Up to now it is only used in metastatic situation.

I.3. Ovarian Ablation/Suppression

The clinical trials of ovarian ablation either by surgical means (open or laparoscopic), or by pelvic irradiation antedate selection by hormone receptor status. However, even so, they demonstrated a reduction in the annual odds of death of 25% for women below 50 years of age at the EBCTCG Oxford overview. Also, in presence of chemotherapy, ovarian ablation adds about 10% to the mortality reduction achieved with chemotherapy alone.

The use of gonadotropin-releasing hormone agonists e.g. Goserelin, appears to provide benefit in the overview analysis. However, it has the advantage of being given for a period of time i.e. 2 years, with return to normal hormonal status after stopping the use of the drug. It can be associated with tamoxifen in premenopausal patients.

Conclusion

Endocrine therapy for breast cancer includes selective estrogen receptor modulators (SERMs), antiestrogenic agents, ovarian ablation by surgical means or pelvic irradiation, and gonadotropin-releasing hormone agonists (LHRH agonists). Up to now, the optimal adjuvant hormonal therapy is considered to be 5 years for tamoxifen for anyone with a tumor that is estrogen receptor or progesterone receptor-positive, even if at a low level, and regardless of the possible concurrent overexpression of Her-2. Patients with tumors lacking estrogen and progesterone receptors will not benefit by tamoxifen administration. Also, for patients with node negative cancers less than 1 cm in diameter regardless of histologic grade, or tumors 1 to 2 cm in diameter of low grade (grade 1), evidence of a benefit exceeding the detriments of systemic adjuvant therapy including hormonal therapy is lacking. However, it seems likely that optimal

therapy will be changed by the new ongoing clinical trials now using the new SERMs, aromatase inhibitors, and LHRH agonists.

II. CHEMOTHERAPY IN EARLY BREAST CANCER

II.1. Current Knowledge on Adjuvant Chemotherapy

The first randomized studies of adjuvant chemotherapy were reported more than 20 years ago by Bonnadona in Milan and the NSABP. Although the regimens were very different, the results of these studies were the same. They showed that premenopausal women may procure a greater benefit from adjuvant chemotherapy than postmenopausal women and that the gain in terms of survival was better for patients with minimal axillary lymph node involvement than for patients with more than 4 involved nodes.

So, for a long time, adjuvant chemotherapy was only given to premenopausal women. Since the results of the meta-analysis, chemotherapy is now known to be also efficient in postmenopausal women. When prolonged chemotherapy is given the risks of recurrence and of mortality is reduced by 35% and 18% in premenopausal women, and 39% and 19% in postmenopausal women respectively.

It is also clear from the last overview meta-analysis that:

1. Polychemotherapy is more effective than single agent chemotherapy,
2. There is no significant greater benefit from prolonging polychemotherapy beyond about 3-6 months,
3. Prolonged benefits of polychemotherapy appear to be largely unaffected by axillary nodes, ER, or menopausal status at presentation, or by the use of tamoxifen,
4. Benefits of polychemotherapy are greater among women aged under 50 years (risk reduction of 36% and 27% for disease recurrence and death respectively), but even at age 50-59, and 60-69 years, polychemotherapy resulted in risk reduction of 19% for disease recurrence and 11% for mortality,
5. Anthracycline-containing regimens are more effective than the CMF regimens, with a benefit of 4% in death rates. There are too few non-breast cancer deaths to assess long-term safety mainly linked with the cardiac toxicity.
6. Taxane containing regimens are more effective than regimens without for N+ patients adding about 3,5% benefit for the disease free survival and 2 to 2.8% for N+ patients..

So, overall adjuvant polychemotherapy has produced risk reduction of 23.4% in disease recurrence, and 14.9% in deaths. This risk reduction was clearer in younger ages, and that polychemotherapy adds to the benefits of tamoxifen and vice versa.

Currently a consensus exists regarding the administration of chemotherapy to women with breast cancer (see appendix I and II). Chemotherapy should be enhanced prior radiotherapy.

II.2. Chemotherapy regimens

Adjuvant chemotherapy regimens that include an anthracycline result in a statistically significant improvement in survival compared to non-anthracycline containing regimens and chemotherapy regimen including taxanes seem of a greater interest.

At present time, there is no role for high dose chemotherapy outside the context of a clinical trial. But dose intensity regimen appears of interest in one trial for N+ operable breast cancers. This fact is not confirmed by others studies concerning locally advanced breast cancer.

AC		X 4 cycles
Adriamycin	60 mg/m ² IV	D1 /3 weeks
Cyclophosphamide	500 mg (or 600 mg?) /m ² IV	D1 /3 weeks
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1. FAC		
5-Fluorouracil	500 mg/m ² IV	
Adriamycin	500 mg/m ² IV	D1 /3 weeks x 6 cycles
Cyclophosphamide	500 mg/m ² IV	
2. CMF		
Cyclophosphamide	600 mg/m ² IV	D1, 8
Methotrexate	40 mg/m ² IV	D1, 8
5-Fluorouracil	600 mg/m ² IV	D1, 8 /4 weeks x 6 cycles
3. FEC 60		
5-Fluorouracil	600 mg/m ² IV	
Epidoxorubicin	60 mg/m ² IV	D1 /3 weeks x 6 cycles
Cyclophosphamide	600 mg/m ² IV	
4. FEC 100*		
5-Fluorouracil	500 mg/m ² IV	
Epidoxorubicin	100 mg/m ² IV	D1 /3 weeks x 6 cycles
Cyclophosphamide	500 mg/m ² IV	
5 A T	50 mg/m ²	
Adriamycin	75 mg/m ²	D1 /3 weeks x 6 cycles
Docetaxel		
6 AC x 4		
+ Paclitaxel	AC (cf supra)	4 cycles
	80mg/mé weekly	X 12
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* Indicated in cases having more than 10 positive nodes.		

Table 9.1. Examples of Chemotherapeutic Regimens used in the Adjuvant Setting

II.4. Tolerance of Chemotherapy

Most of the cytotoxic drugs and combination regimens used in breast cancer are with a spectrum of toxicity, but hematological toxicity with neutropenia, thrombocytopenia and anemia is by far the most frequent. Complete blood counts are required before each cycle to verify bone marrow recovery.

Hospitalization with broad-spectrum antibiotics should be mandatory in cases of febrile neutropenia, whereas WHO grade IV thrombocytopenia and anemia may require platelet or red cell transfusions. Other toxicities include nausea and vomiting which are now readily managed with the advent of 5-HT₃ antagonists; cardiac failure due to high cumulative doses of anthracyclines (>500 g/m² for doxorubicin); alopecia which is frequently unpopular among young women and, menstruation disorders which are mainly transitory in women < 40 years but frequently definitive in women over 45 years. Neurological toxicity can be observed with use of taxanes. Finally, about 50 to 60% of women receiving adjuvant chemotherapy may gain weight, the mechanism of which is unknown.

In practice, several measures are recommended for adequate monitoring of chemotherapy: a complete blood cell count before each cycle, left ventricular function evaluation before the initiation of chemotherapy, the use of a central venous catheter to prevent extravasation of cytotoxic drugs and adequate contraception (excluding estrogens) to avoid pregnancy and fetal risks during therapy.

II.5. Predictive Markers for Response to Chemotherapy

There are many factors associated with a poor prognosis, and these are useful to guide systemic therapy. Predictive factors, on the other hand, help determine the probability of response to a particular drug or drug class.

Although application of these factors in choosing the appropriate systemic chemotherapy for a certain patient appears promising, currently there is no clinical level 1 evidence to support the definitive predictive role of any tumor or patient characteristics for response to cytotoxic therapy. It is now well established that invasive lobular carcinomas are less sensitive to chemotherapy than invasive ductal carcinomas.

However, some markers hold some promise. Analysis of retrospective data suggests that Her-2 overexpression may indicate particular sensitivity to anthracyclines, and less responsiveness to CMF. So, many prospective trials are now exploring these unconfirmed data. p53 represents another potential predictive factor as there are some preclinical and clinical data to suggest that tumors with p53 mutations may be particularly sensitive to taxanes and relatively resistant to anthracyclines. Tumors with amplification of the topoisomerase II alpha gene seem more sensitive to anthracyclins regimens. Other markers include urokinase plasminogen activator, tissue plasminogen activator inhibitor 1, , thymidylate synthase, MDR-1 overexpression, and alterations in Ki67 and p27 genes. Exploration of the role of all these markers may help in the future to determine the most appropriate treatment for a particular patient.

III Targeted therapy :

For patients with HER2/neu overexpression reports of some trials in 2005, and subsequent reports demonstrate that an humanized antibody trastuzumab (Herceptin) (administered every 3 weeks during 1 year) following chemotherapy improves clearly both disease free survival and overall survival.

Side effects : In 2-7% of cases, trastuzumab is associated with cardiac dysfunction . As a result, regular cardiac screening with either a MUGA scan or echocardiography are mandatory during the trastuzumab treatment period. Approximately 10% of patients are unable to tolerate this drug because of pre-existing heart problems;

Many questions are still unresolved concerning this type of treatment

- 1) Duration 1 year or shorter duration ?
- 2) The use of trastuzumab associated with anthracycline containing regimen appears to increase the risk of congestive cardiomyopathy. Is it possible to select patients who could benefit of an association of trastuzumab and a non-anthracycline-based regimen?
- 3) Should trastuzumab, in adjuvant situation has to be used with or following adjuvant chemotherapy ?
- 4) Do we have to use trastuzumab for tumors < 1cm?

New targeted therapy are effective on metastatic breast cancers (for lapatinib a novel inhibitor of HER1 and HER2) instance now disponible could have a place in adjuvant situation in addition with trastuzumab.

ADJUVANT SYSTEMIC TREATMENT

As mentioned above in the results of the overview meta-analysis of EBCTCG, adjuvant tamoxifen and adjuvant chemotherapy trials have demonstrated that each of these modalities, used in appropriate patient groups, will greatly reduce the annual odds of recurrence and mortality, and that such treatments are not mutually exclusive i.e. polychemotherapy adds to the benefits of tamoxifen and vice versa.

However, other analyses and results of some individual trials have suggested that the added benefits from adjuvant chemotherapy may be considerably smaller in those cases with ER-positive tumors specially when treated with optimal endocrine therapy. These suggestions are most apparent in recent tumors specially when treated with optimal endocrine therapy. These suggestions, however, have not appeared in recent Intergroup and NSABP trials.

In the future, it is possible that LHRH agonists and aromatases inhibitors may replace chemotherapy as an adjuvant therapy of pre- and postmenopausal patients, respectively, with receptors-positive tumors.

II.3. Neo-adjuvant Chemotherapy in Breast Cancer

Neoadjuvant chemotherapy is the use of cytotoxic drugs prior to local treatment. There are several possible advantages with this strategy. Some non-randomized and randomized studies suggest that a reduction in tumor volume in response to primary chemotherapy may limit the extent of surgery required, and particularly the need for mastectomy. But long-term data confirm that less mutilating surgery permit higher local failures without detrimental effect in term of overall survival.

A second objective of neoadjuvant chemotherapy is the early eradication of micrometastases. Any tumor response indicative of chemosensitivity will render aggressive therapy including intensification of chemotherapy conceivable in order to improve survival. Finally, neoadjuvant chemotherapy may inactivate tumor cells and thereby possibly prevent their dissemination during surgery.

In clinical practice, neoadjuvant chemotherapy procures a high clinical and radiological response rate, (higher than 80% in most studies, with a complete response rate of about 20%). As mentioned above this high response rate, and the need for mastectomy after neoadjuvant chemotherapy, as a primary surgical approach is questionable. Currently, conservative surgery is possible after chemotherapy in about 50% to 75% of women who would have been candidates for mastectomy. Most authors recommend 3 to 6 cycles of neoadjuvant chemotherapy with various drug combinations. The FAC or the FEC regimens or regimen including taxanes mainly used. For patients with HER2/neu surexpression , addition of tratstuzumab improves the results. In some studies a complete histological response is, but a good pronostic factor (réfarence Aberdeen) but this data was not confirmed by the randomized trial NSABP .

In patients with expression of hormonal receptors the neoadjuvant systemic treatment can be an hormonal therapy. This schedule is often preferred in old patients for which neo-adjuvant chemotherapy could be detrimental.

LATE AND LONGTERM COMPLICATIONS AFTER ADJUVANT THERAPIES OF BREAST CANCER

A particularly important trend has been the increasing application of systemic adjuvant therapies to patients with earlier stage disease even with a lower risk of breast cancer recurrence. Although this strategy extends the absolute benefits of adjuvant therapy to more women, it also exposes a greater proportion of those women with breast cancer to the potential of late complications of adjuvant therapy.

A. Ovarian Failure

Premature menopause is a common outcome after adjuvant therapy in menstruating women. In parallel, hormone replacement therapy is routinely discontinued at the time of diagnosis in postmenopausal patients.

Age and the duration as well as the type of adjuvant therapy are the primary determinants of ovarian failure. The median time to its onset is shorter in older than in younger women (2-4 months vs. 6-16 months). Ovarian failure is less likely to be reversible in older women ($\approx 10\%$ vs. up to 50%). The rate of permanent ovarian failure is lower with regimens like AC than with CMF. Treatment with CMF for 6 months results in permanent ovarian failure in 70% of women over 40 years of age and in 40% of younger women. Short and longterm effects of menopause in breast cancer survivors include the following: A-ton des données pour les taxanes ?

1. Vasomotor symptoms

Hot flushes, night sweats, disruption of sleep and irritability may occur in certain situations including postmenopausal patients who are taken off hormone replacement therapy, or started on tamoxifen, and in premenopausal patients who have received adjuvant chemotherapy, or undergone ovarian ablation. These symptoms may occur very early during the course of the disease and its treatment, or may occur many years after treatment. They may be transient, or may be severe and persistent.

2. Vaginal effects

In a study on breast cancer survivors, vaginal dryness was significantly increased in women who had received any form of adjuvant therapy compared to those who had not received adjuvant treatment. Vaginal dryness may lead in some patients to dyspareunia. Also, vaginal discharge was increased in women who received adjuvant tamoxifen but not in women who received chemotherapy alone.

3. Osteoporosis

Ovarian failure early menopause and anti-aromatase treatment in post menopausal patients is a risk factor for osteoporosis increase the risk of osteoporosis. Long term data on fractures in women with chemotherapy-induced ovarian failure are unavailable. To prevent this complication women should have adequate dietary intake of calcium and vitamin D and should perform weight-bearing exercises regularly and have their bone density evaluated. Treatment with bisphosphonates mitigates bone loss in women with breast cancer and chemotherapy-induced ovarian failure. On the other hand, tamoxifen when given as adjuvant therapy preserves bone mineral density in postmenopausal women, but whether it reduces the risk of vertebral or hip fractures is uncertain. However, tamoxifen may increase bone loss in premenopausal women because of its estrogen-antagonist activity.

The administration of estrogen to women with breast cancer for the relief of menopausal symptoms and for the long-term prevention of osteoporosis is contraindicated

B. Cardiovascular Disease

Related with chemotherapy

An important unanswered question is the effect of the induction of premature menopause associated with adjuvant treatment on the cardiovascular system. Long-term studies are essential to evaluate this concern, but preliminary lipid profiles, blood pressure measurements, and waist to hip ratio measured in one study

of breast cancer patients treated by adjuvant therapy at age 50 years and younger, do not show significant differences among women who received adjuvant therapy and no therapy.

Doxorubicin directly damages the myocardium and can cause cardiomyopathy. However, when the total dose of doxorubicin is limited to 240–300 mg/m² the incidence of clinically important cardiomyopathy is less than 1%. However, in one study 8% of those receiving adjuvant doxorubicin had echocardiographic evidence of systolic dysfunction or reduced LVEF, compared to less than 1% of women treated with CMF regimen. Whether such subclinical systolic dysfunction will result in clinically overt cardiac problems is unknown. Dexrazoxane (cardioxane) as preventive treatment can should be used when a total dose of adriamycin reaches more than 300 nmg/m² (more for epirubicin)

Related with hormonal treatment

On the other hand, a potential benefit of adjuvant tamoxifen therapy may be a reduction in cardiac mortality in postmenopausal women treated with tamoxifen, serum concentrations of total and LD lipoprotein cholesterol fall by about 10%. Whether tamoxifen reduced the rate of cardiovascular disease remains to be determined. Retrospective analysis of two randomized trials showed that the risk of myocardial infarction, and death from cardiac causes were lower among women who received tamoxifen than among those who did not. However, the NSABP P-1 tamoxifen prevention trial results did not show such a protective effect.

On the other hand, women treated with tamoxifen have small decreases in plasma concentration of antithrombin III, protein S, and fibrinogen. The relevance of these findings to the observed very small excess risks of DVT, pulmonary embolus, and stroke among postmenopausal women taking tamoxifen is unknown yet. Also, it was observed that concurrent administration of tamoxifen and chemotherapy may result in a higher incidence of venous and arterial thrombosis than either treatment alone.

C. Cognitive Dysfunction

Two or three years after adjuvant treatment, problems with concentration, memory and language were observed to be more frequent in women receiving chemotherapy than in other women. The mechanism of this cognitive dysfunction is unknown, but it has been postulated that a direct effect of chemotherapy or diminished estrogen secretion due to ovarian failure has a role.

D. Second Cancers

Tamoxifen treatment is associated with about 80 excess cases per 10,000 of endometrial cancer at 10 years, primarily in women over the age of 50 years. There is no evidence that tamoxifen therapy increases the risk of other cancers. In most of cases, endometrial cancers are of low grade and early stage that are curable with surgery alone. There is little evidence that the risk of second cancer is increased among women who receive adjuvant CMF chemotherapy. Also, there is less information on the risk of second cancers among women treated with doxorubicin-containing regimens, and there is no information on the risk with those containing taxanes. The risk associated with 6 months CMF therapy includes acute myeloid leukemia or myelodysplasia (5 excess cases per 10,000 treated patients at 10 years). Mitoxantrone used as adjuvant treatment increases the risk of secondary acute leukemia and combined chemotherapy and radiotherapy may increase the risk of leukemia.

E. Neurologic Toxicity, Weight Gain, Fatigue and Quality of Life

The taxanes cause both sensory and motor peripheral neuropathy, myalgia and arthralgia. In rare cases, tamoxifen is associated with reversible retinopathy and slight increase in cataracts. Tamoxifen is frequently thought to cause depression and weight gain, but both were similar in incidence in tamoxifen

and placebo groups in several trials. On the other hand, the majority of women with breast cancer who are treated with CMF regimen gain weight while women treated with AC combination gain less weight than those treated with CMF. Weight gain may adversely affect the quality of life. Also, many women with breast cancer who are receiving adjuvant chemotherapy have fatigue. The fatigue appears to resolve after treatment. So, measurements of the quality of life worsen during adjuvant chemotherapy but improve after the cessation of treatment. This may be also attributable to other factors including depression, body image, sexual dysfunction and other treatment related factors.

Late Effects of Radiotherapy

Long term side effects of irradiation of the breast, chest wall and regional lymph nodes include cardiac toxicity, second cancers, pneumonitis, lymphedema, brachial plexopathy, skin reactions, and rib fractures.

Meta-analysis and registry based studies have shown small long-term increases in mortality from cardiac causes involving coronary artery disease. However, most of these women have been treated with outmoded techniques that exposed the heart to high doses of radiation. Women treated with modern techniques have not been found to suffer from an increased risk of these cardiac complications. However, even when radiation fields are limited to the breast, there still may be a risk of cardiac toxicity when the daily doses are high implicating probably an adverse systemic effect of radiotherapy. Sequentially administered radiotherapy and doxorubicin with higher single doses (75 mg/m²) or higher cumulative doses (450 mg/m²), also increases the risk of cardiac toxicity.

Several case-control studies have found that the risk of contralateral breast cancer was slightly increased among patients treated with radiotherapy after mastectomy, probably as a result of the small dose of scatter radiation to the other breast. Sarcomas are very rarely caused by irradiation. Likewise, angiosarcomas of the skin of the irradiated breast occur in 0.1% to 0.5 % of patients. Also, in case-control studies that were mainly limited to smokers, there were very small excess risk of ipsilateral lung cancer, and esophageal cancer among women treated with now outmoded radiation techniques. Symptomatic radiation pneumonitis occurs in about 1% of women. This incidence is higher when chemotherapy and radiotherapy are given concurrently or when a supraclavicular or full axillary field is treated as well.

Pregnancy after Breast Cancer

A significant sector of new cases of breast cancer occurs in women of childbearing age and it is natural after completing therapy for the patient to ask about an integral and treasured part of life; pregnancy and childbearing. Although hormonal influence on carcinogenesis, growth rate and metastases of breast cancer is well known, few studies have evaluated women who became pregnant after breast cancer treatment.

There are several retrospective and population-based studies that have been published. Also an ongoing study in the USA will help to address this issue. From all the retrospective studies, it has been generally observed that breast cancer patients who subsequently become pregnant have good survival rates, often the same or sometimes better than patients with no subsequent pregnancy. Three of these retrospective studies have examined the timing of subsequent pregnancy on breast cancer prognosis. In one study patients who became pregnant within 6 months had a comparatively poor prognosis than those who waited 6 months to 2 years to become pregnant after breast cancer diagnosis (5 year survival rates of 54% vs. 78% respectively). Those who waited 5 years or more to become pregnant had a 100% 5-year survival rate from that point. However, these data may be affected with the fact that the longer survival after diagnosis is in itself an indicator of the patient's better prognosis regardless of the occurrence of pregnancy or not. Although smaller, the other two studies did not find, however, a statistically significant difference between outcomes of patients based on the time interval between diagnosis and pregnancy.

However, certain biases remain inherent in these retrospective studies. For example, as pregnancy is not considered as a disease, it may be noted or added in a patient's chart. So, four large population-based studies have been published worldwide since 1994 from Finland, Sweden, Denmark and USA. Again all these studies showed that survival of women with breast cancer is not decreased in any of these reports. Still, it is likely that breast cancer patients who choose to become pregnant and give birth were disease-free as opposed to an unknown proportion of controls that had a recurrence at the time of matching for the study, but had not yet died. For this reason, as well as other factors that may affect data interpretation, a prospective study on pregnancy after breast cancer treatment is now being conducted in the USA and funded by the Army Breast Cancer Research Fund.

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Till page 171