



CONTINUING EDUCATION PROGRAM: FOCUS...

The management of breast cancer



M. Espié

Department of Medical Oncology, Breast Diseases Center, Saint-Louis Hospital, Paris Public Hospitals Health Service, 1, avenue Claude-Vellefaux, 75475 Paris cedex 10, France

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Abstract Because of its prevalence, breast cancer is a major public health problem although its prognosis has improved as a result of early screening and improvement in treatments. We now no longer refer to breast cancer in the singular, but to breast cancers, which have different prognoses and treatments depending on their molecular profile.

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Epidemiological findings, a few figures

Because of its prevalence, breast cancer is still a major public health problem. It has been estimated that 53,000 women suffered from it in France in 2012 [1]. Incidence of breast cancer in France and that it killed more than 11,000 people. Its incidence is low under the age of 30-years-old and then increases up to the age of 60–69-years-old when it is over 320 per 100,000 women per year. Rates fall slightly after the age of 85-years-old (245 per 100,000).

These figures make breast cancer the leading cause of cancer deaths in women with an estimated figure for 2012 of 11,289 deaths in France. Death rates increase with age from 10/100,000 women between 35 and 40-years-old to 80/100,000 at around 65-years-old, 102/100,000 between 70 and 74-years-old and 245 per 100,000 over 85-years-old. Of these 11,289 women who died from breast cancer in France 1075 were under 40-years-old and 4113 were under 65-years-old [2]. These figures highlight the magnitude of the problem in postmenopausal women, particularly as the mortality rate is continuing to increase, mostly in elderly women. Five-year survival has been estimated to be 86%, compared to a 10-year rate of 76%.

E-mail address: marc.espie@sls.aphp.fr

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Locoregional treatments

Surgery remains the main treatment for breast cancer. Changes in surgery have included a reduction in the indications for mastectomy (which is still however occasionally necessary) and an increase of conservative treatments, particularly incorporating plastic surgery techniques into breast surgery (oncoplasty), which allows more bulky tumors to be excised. Initial (neoadjuvant) chemotherapy can also make surgery more conservative by reducing tumor volume. In parallel to this increase in conservative treatment, the 'sentinel lymph node' technique has emerged, which allows the initial axillary lymph nodes, which are most likely to be diseased, to be removed without carrying out axillary curettage if these lymph nodes are not invaded. This technique therefore helps to reduce the adverse effects of axillary curettage, and particularly the risks of lymphedema. It requires pre-operative injection of a blue dye and a radioactive isotope around the tumor or areola. This dual technique helps to reduce the risk of false negative results [3].

Treatment intensity may also be reducing in radiotherapy. In conservative treatment, the general rule is to irradiate the whole breast with additional radiotherapy to the tumor bed and irradiation of the lymph node regions if these are diseased. Changes in radiotherapy dose and methods are being studied in some patients and partial breast irradiation is occasionally being offered (elderly patients and small, relatively non-aggressive tumors) [4].

Reconstruction surgery has also advanced in patients with mastectomy, with the development of same stage reconstruction techniques although these are not always possible and need patients to fully understand that their breast will not return to what it was before, together with advances in mucocutaneous and skin and fatty tissue flaps (DIEP¹) [5].

Prognostic indicators for breast cancer and poor prognostic indicators for response to treatments

In addition to the conventional prognostic indicators (size of tumor, lymph node invasion, grade and age), in recent years, hormone-receptors (estrogens and progesterone) and overexpression of HER2 (or CerbB2) (an epithelial growth factor) reflecting self-encasement of the tumor have been added. The Ki67 test is also useful as this can quantify cellular proliferation (the Ki-67 labeling index represents the percentage of nuclei stained by the Ki-67 antibody). Genomic tests are currently being developed with the aim of analyzing each tumor to 'predict' its prognosis and also to determine whether adjuvant chemotherapy or hormone therapy are or are not essential. The concept of breast cancer is now increasingly being broken down and several tumor subtypes have been identified:

- luminal A cancers: these are breast cancers which carry a good prognosis, progress slowly and strongly express estrogen and progesterone receptors. They do not overexpress HER2 and are therefore ER⁺⁺⁺, PR⁺⁺⁺, and CerbB2

negative. These are the relatively non-proliferative hormone dependent tumors, which often do not require chemotherapy, particularly if the Ki67 index is under 10%;

- luminal B cancers: these carry a less good prognosis than luminal A, are less hormone-sensitive, and often have a higher Ki67 index. Some may be associated with HER2 overexpression and the combination of chemotherapy and hormone therapy is often required together with trastuzumab (Herceptin) if HER2 is overexpressed;
- HER2 cancers: these are aggressive breast cancers, which carry a poor prognosis. They are estrogen and progesterone receptor negative and their HER2 overexpression is graded ⁺⁺⁺. These cancers require chemotherapy combined with trastuzumab which has changed their poor prognosis;
- 'triple negative' cancers: these are also poor prognosis cancers, which are completely undifferentiated and are estrogen and progesterone receptor negative. They do not overexpress HER2 (ER⁻, PR⁻, HER2⁻) (Figs. 1 and 2).

There is other less common subtypes, which are still being studied and gene analysis (genomics) is developing. This can be used to characterize tumor genes, and to test for amplifications, mutations and the level of expression (gain or loss) of a given gene. Apart from the genes involved in hormone-receptors and HER2 expression, other genes are being examined which are involved in invasion, and interactions with the tumor stroma, etc. It is hoped that by guiding treatment and predicting sensitivity to treatments an attempt can be made to individualize them to avoid chemotherapy, which is of no benefit for one person whereas it may be essential for another. Several tests have been developed: the Mammaprint which is a test performed from a DNA probe which shows the expression of 70 genes, Oncotype DX which shows 21 genes, and genomic grade, which is an analysis of the expression of 97 genes on frozen samples, etc. These tests incorporate a number of different genes although, overall and apart from hormone and HER2 receptors, these are mostly genes involved in proliferation. They have not as yet been shown to be more effective than conventional immune-histochemical indicators. Prospective studies are therefore ongoing and we should have an answer to the question of their actual utility in a few years. They have however been validated in retrospective studies and do identify groups with a good or bad prognosis. They do not have marketing authorization in France pending their possible validation in the ongoing prospective studies.

Adjuvant treatments: chemotherapy, hormone therapy, targeted therapies

Changes in chemotherapy

In the 1980s, chemotherapy was often restricted to patients whose tumors were associated with lymph node invasion, although metastases were found for 20 to 30% of tumors when lymph node invasion was not present. It was therefore extended to forms of the disease without lymph nodes invasion, which carried a poor prognosis (large size, grade II or III, vascular emboli⁺, or negative hormone-receptors).

¹ DIEP: deep inferior epigastric.

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