

Beside explaining the occurrence of unexpected breast cancer among very young patients, one would have thought genetics may highlight certain specific phenotypic, biologic and behavioural characteristics of breast cancer among the youngest. Indeed, BRCA1-linked breast cancer shares certain specific characteristics with that of young women, such as a high grade, high proliferation rates and the frequent absence of hormone receptors. As well, recent descriptions of gene expression profiles appear similar and might plead for a common stem cell progenitor. However, although this remains controversial, genetics do not appear to account for the high prevalence of local recurrence of breast cancer in the populations of young women. We showed that among breast cancer patients with a strong family history and treated with conservative surgery, young age remained the only risk factor of local relapse, whereas the presence of a BRCA1/2 mutation was not.

We will discuss on the bases of recently acquired knowledge, the specific care of young carriers of BRCA1 or BRCA2 mutations, as well as the care of very young women affected with breast cancer, whether genetically-determined or not.

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Early breast cancer in very young women: the interphase between endocrine and chemotherapy treatment

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One in forty women with breast cancer is very young (<35 yrs). Outcomes in this age group have unique aspects. St Gallen Guidelines on Early Breast Cancer exclude women <35 from minimal risk category because of higher relapse risk.

IBCSG found women <35 yrs had higher risk of relapse after adjuvant CMF with 10 yr DFS of 35% which was significantly worse than 47% in older premenopausal women [1]. The relapse rate in women <35 yrs was particularly high in ER+ve group, who had a worse outcome than women <35 yrs with ER-ve tumors (10 yr DFS in <35 yrs: ER+ve = 25%, ER-ve = 47%). When US groups studied trial outcomes, a similar pattern was seen [2]. For ER-ve tumors, the outcome in women <35 yrs was similar to the older premenopausal women.

In premenopausal women with ER+ve cancer who receive chemotherapy, the outcome is better if amenorrhea occurs. The poor outcome for very young with ER+ve tumors treated with chemotherapy alone, maybe due to failure to achieve endocrine benefit of amenorrhea in this age group.

Adjuvant ovarian ablation is effective in women <50, but if chemotherapy is also given, ovarian ablation is of uncertain benefit [3]. The data are mainly from women aged 40–50 yrs who become menopausal from chemotherapy. This may underestimate benefit for very young.

US Intergroup randomized premenopausal receptor positive women to CAF, CAF + goserelin, or CAF + goserelin + tamoxifen. There was no significant benefit overall with addition of goserelin [4]. Retrospectively the subgroup <40 yrs appeared to benefit from goserelin. IBCSG randomized premenopausal women to CMF, or goserelin, or CMF then goserelin [5]. Goserelin after CMF resulted in a non-significant benefit. In an unplanned analysis, it appeared the ER+ve subgroup <40 yrs derived benefit from goserelin after CMF.

US groups assessed outcomes of very young ER+ve women compared with their older premenopausal counterparts, from trials with chemotherapy followed by tamoxifen. The results suggest an increased relative risk for those <35 yrs [2].

Very young women with receptor positive cancer deserve attention because of their poor outcome. Optimal chemo-endocrine strategies will be tested in a suite of 3 trials (SOFT, TEXT and PERCHE) led by IBCSG and joined by Breast International Group (BIG) and North American Breast Intergroup.

References

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Mastectomy: the preferred treatment in young women?

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Nowadays, breast-conserving therapy is a generally accepted and widely embraced treatment modality for the majority of patients with early-stage breast cancer. Trials comparing breast-conserving therapy versus mastectomy revealed comparable results with respect to overall survival. However, several studies demonstrated the influence of young age as an independent risk factor of poor disease outcome. Patients with breast cancer diagnosed at younger age present more frequently with factors associated with a poor prognosis, such as larger tumours, vascular invasion, high-grade tumours, lymph node involvement, negative hormone receptors, and tumours with high S-phase fractions and overexpression of p53. In addition, young age has also been shown to be an independent risk factor. So the question arises whether breast-conserving surgery is justified as a treatment option in the management of early-staged, young breast cancer patients.

Randomised-controlled trials that studied mastectomy versus breast-conserving surgery without radiotherapy indeed showed a difference in overall survival in favour of more aggressive surgery. It is assumed that local recurrence after breast-conserving therapy arises from tumour cells that are left in the breast after local excision. Apart from the emotionally devastating events of any recurrence for the patient, distant metastasis may develop as a result of local recurrence. Furthermore, tumour bed re-excisions are performed more frequently in the younger age group, although no differences are observed in the final negative margin status among the other age groups. This might indicate the difficulties encountered when trying to achieve negative resection margins in younger patients and suggesting the presence of an extensive intraductal component or multifocal disease in younger women. Remarkably, no trials exist whom specifically compare breast conservative surgery versus mastectomy in women diagnosed at young age. A meta-analysis of three randomised EORTC-trials 10801, 10854, and 10902 revealed that patients of 35 years and younger diagnosed with breast cancer not only have almost three times higher local recurrence rates, but also a lower survival rate. However, adjuvant radiotherapy demonstrated very similar survival patterns when compared to mastectomy alone and seems to reduce the risk of local recurrence. Especially in women with early-onset breast cancer, perioperative chemotherapy demonstrated also a reduction of local recurrence rate. To date, no clinically useful risk factors for local recurrence have been identified within the population of young breast cancer patients. This is an important area of breast cancer research; especially gene expression profiling using microarray analysis is a promising method to investigate this problem.

But should adjuvant treatment compensate for possibly inadequate surgery? After all, adjuvant radiotherapy trials have also demonstrated a beneficial effect for radiotherapy on overall survival after mastectomy in early breast cancer patients. Patients with limited nodal involvement benefited more from adjuvant radiotherapy than patients with extensive nodal disease. Although excessive radiation and chemotherapeutic regimes are obsolete, the long-term effects on in particular cardiovascular disease have to be taken into account when planning an optimal strategy in young breast cancer patients.

Finally, women with early-onset breast cancer are more likely to harbour one of the breast-cancer susceptibility genes, BRCA1 or BRCA2, or to have another genetic predisposition. Overall, the prognosis of breast cancer in carriers of a BRCA1- or BRCA2-mutation seems to be similar to that in age-matched patients with so-called sporadic breast cancer. In addition, since normal BRCA1/2 function may be associated with DNA repair, the possibility of an increased rate of radiation-induced malignant disease in carriers of BRCA1/2 mutations has been raised. An international collaboration study found no significantly increased rates in local recurrence after 10 years when comparing breast-conserving therapy in women with germline BRCA1/2 mutations to matched sporadic controls. However, it is noteworthy that significantly higher rates of contralateral events are observed in the genetic predisposed group. Bilateral mastectomy has demonstrated a substantially reduction of subsequent breast cancers in this group of patients. Although no evidence exists that overall or disease-specific survival is impaired by opting for conservative treatment, careful monitoring will be necessary for early detection.

The management of young women with newly diagnosed breast cancer still remains a challenging problem with complicated medical, psychological, and social implications. Although eventually breast-conserving therapy is regarded as the prime option, mastectomy and subsequent