Adjuvant chemotherapy for local relapse breast cancer

Patients with isolated locoregional recurrences of breast cancer have a high risk of distant metastasis and death from cancer.[1] The main objective in this clinical setting is curative treatment, which consists of radical surgery with or without complementary radiotherapy. The targeted localisations include soft tissue of the ipsilateral conserved breast or of the chest wall, mastectomy scar or skin, and lesions in the ipsilateral axillary lymph nodes, extranodal soft tissue of the ipsilateral axilla, or ipsilateral internal mammary. Adjuvant chemotherapy reduces the risk of recurrence after primary breast cancer, therefore it follows that adjuvant chemotherapy should also decrease the risk of recurrence in patients with completely resected locoregional recurrence of breast cancer. However, few randomised trials have investigated the effect of adjuvant chemotherapy in this setting.

Unfortunately, several randomised trials, including those of EORTC, and German (GBSG-6) and French (PACS 03/0003) collaborative groups, have prematurely closed before completion of accrual because of a low rate of inclusion. Oncologists might have felt uncomfortable randomly assigning patients with a high risk of recurrence to no chemotherapy, despite the absence of evidence for the use of chemotherapy in this clinical situation.

Having overcome this enrolment issue, the CALOR trial[2] is the first randomised trial to provide evidence for the role of chemotherapy in this subset of patients. Presented by Stefan Aebi and colleagues[2] in *The Lancet Oncology*, the CALOR trial is a clinically meaningful study. The protocol design was straightforward and pragmatic, with surgical procedures, radiation therapy, and chemotherapy administered according to the treating clinician's preferences. Patients were randomly assigned to either adjuvant chemotherapy or no adjuvant chemotherapy (follow-up only). Nevertheless, recruitment was challenging, and the investigators should be praised for their resilience. The initial sample size needed was almost 1000 patients, but was later amended to 276, and the study was terminated with a final enrolment of 162 after a recruitment period of nearly 7·5 years.

The ability to draw conclusions from a study with such a reduction in sample size is questionable. However, the steering committee of the trial cleverly amended the initial statistical plan to a single, final time-driven analysis. This amendment was done before any data analysis comparing treatment groups was done, and the revision was therefore not biased to treatment differences. Under the protocol amendment, the entire 0·05 alpha was reserved for this final analysis. Despite the reduction in sample size, the value of this analysis is undeniable, and the magnitude of the observed effect is very large and statistically significant.

Aebi and colleagues[2] concluded that adjuvant chemotherapy should be recommended for patients with completely resected isolated locoregional recurrences of breast cancer, especially if the recurrence is oestrogen-receptor negative. This conclusion emphasises the clear benefit for patients with oestrogen-receptor negative recurrences; however, the interpretation of the results in the overall population might be limited. The uncertainty about the overall conclusion is due to a marginally significant test of interaction between oestrogen-receptor status and treatment effect ($p_{interaction}$=0·046), which suggests that the treatment effect is heterogeneous according to oestrogen-receptor status. Reporting of an overall result in the presence of a significant interaction is debatable; therefore, reporting of the findings and their interpretations for both subgroups separately might be a valuable alternative.[3] The overall benefit seems to have been driven largely by the oestrogen-receptor-negative subgroup, but the interaction test only suggests—rather than proves—that the benefit of chemotherapy is likely to be larger for the oestrogen-receptor-negative subgroup than for the rest of the population, and the sample size was too small, with too few events, to claim that chemotherapy had no benefit in the oestrogen-receptor-positive cohort.

To derive conclusions from overall results only rather than to take subgroup analysis into account when an interaction is observed has its pros and cons.[4] Following Aebi and colleagues' conclusions, based on the overall results of the CALOR study, subsequent trials wanting to assign patients in this setting to no chemotherapy will be impossible. However,



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whether chemotherapy has any benefit for patients with oestrogen-receptor-positive recurrence is still unclear. Decisions with regard to the use of adjuvant chemotherapy for locoregional recurrences should follow the same algorithms as used for the adjuvant indication in early breast cancer. In this situation, the use of genomic signatures could be of interest. Further information could be gained from retrospective investigation of the value of genomic signatures in the subgroup of patients with oestrogen-receptor-positive tumours in this prospective trial. The results could help to define the likelihood of receiving a benefit from adjuvant chemotherapy in this setting, and would add to the findings of the CALOR trial.

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I declare that I have no conflicts of interest.

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