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Short Communication

Conservative local treatment *versus* mastectomy after induction chemotherapy in locally advanced breast cancer: A randomised phase III study (EORTC 10974/22002, LAMANOMA) – Why did this study fail?

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The optimal management of patients with locally advanced breast cancer (LABC) remains undefined. It is currently generally accepted that the administration of chemotherapy before locoregional treatment results in high response rates and improved locoregional control, the latter being the major goal of therapy. The question of whether the combination of (modified) radical mastectomy and radiotherapy is necessary in maintaining locoregional control, however, remains unresolved. The possibility of breast conservation was demonstrated in prospective non-randomised studies and in two small inconclusive randomised trials performed in the 1980s [1,2].

In view of this persistent controversy, it was clinically relevant to answer the question of whether mastectomy can safely be replaced by breast-saving procedures in patients with LABC. This issue was the subject of EORTC 10974/22002 (LAMANOMA) study. The main objective of this study was to show that breast-conserving treatment (radiotherapy alone or tumourectomy followed or preceded by radiotherapy) is not inferior to mastectomy plus postoperative radiotherapy in terms of overall survival (primary endpoint), time to locoregional failure and quality of life (secondary endpoints) in LABC patients who first received induction chemotherapy. Major eligibility criteria in LAMANOMA included LABC at presentation (T3–4, N0–N2, M0; any T, N2, M0; inflammatory breast cancer), prior induction chemotherapy (standard or investigational regimens), and eligibility for both conservative local treatment and mastectomy plus radiotherapy at the time of randomisation. Breast conserving treatment (BCT) included a choice of one of the three therapeutic options: radiotherapy alone, tumourectomy followed by radiotherapy or tumourectomy preceded by radiotherapy. The type of local conserving management was tailored individually, but each institution had to describe upfront its policy for BCT. To show that breast-conserving treatment is not inferior to mastectomy plus postoperative radiotherapy (a hazard ratio of less than 1.20), 1210 patients (605 per arm) were required to be randomised over a period of 5 years.

The study was opened in October 2001. Although numerous institutions offered their support, the study faced serious problems with patients' accrual. Initially, 47 institutions from 21 countries representing four international co-operative groups declared their participation. Subsequently, 17 institutions were found ineligible for various reasons, leaving 30 institutions potentially interested and eligible. It was estimated that these 30 institutions together should be able to enter 242 patients per year in the trial. Finally, however, only 11 centres from five countries actually opened accrual. The total number of patients enrolled over a period of 21 months was only 23, about one per month instead of the estimated 20 per month. Hence, the study was closed due to insufficient accrual.

In order to clarify the reasons precluding centres' participation we designed a questionnaire including 20

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specific questions, of which 10 inquired about the causes of low patient accrual (more than one answer was allowed) and the remaining 10 asked about competing studies and standard therapeutic strategy used in the centre in LABC. The 30 institutions that initially declared participation and were eligible for participation were sent this questionnaire and 25 (83%) returned it. The most common answer was that the institution decided to stand by its own current therapeutic strategy (seven institutions), most frequently (six institutions) depending on response to primary chemotherapy. Other answers were the following: the lack of consensus on participation in a local team (six institutions); large proportion of patient refusals (five institutions); ethical and/or logistical problems (five institutions); too few patients with LABC (five institutions); another study in LABC (one institution); and other causes (eight institutions).

We failed to detect any dominant reason for this study's failure. It is well known that physicians tend to overestimate the potential accrual of their institutions to trials. This has various causes, for instance not all eligible patients give informed consent, or not all attending doctors may be aware of the trial, and hence do not explain it to the patients. This aspect of clinical trial methodology is particularly relevant in diseases that are being treated in a multidisciplinary fashion, for example breast cancer. If a patient is informed by her surgeon about the treatment plan, including chemotherapy followed by mastectomy (the 'gold standard'), it may be difficult afterwards to offer her participation in a trial that has another option, breast conservation. On the other hand, if a patient is informed by her surgeon that primary chemotherapy may result in tumour regression allowing breast conservation, she is likely to refuse participation in a trial where mastectomy is still an option.

It is of great importance to find ways to predict failures in future studies, as a lot of resources could be saved for other purposes. As for the basic question of the trial: as to whether radical surgery can safely be avoided in the framework of multimodality treatment consisting of primary chemotherapy, (limited) surgery, radiotherapy, and endocrine adjuvant therapy if applicable, we still do not know.

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