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Editorial Comment

Editorial comment on 'Serum markers in breast cancer management'

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Conventional serum tumour markers are antigen-based, e.g. MUC1 mucin detected as CA15.3. Their roles in breast cancer management include screening and early diagnosis of primary disease, prognostic value, monitoring of primary disease after surgery, and the diagnosis and monitoring of metastatic disease; they have the advantages of being simple, objective, reproducible and cost-effective. While some of these roles remain to be defined, others have been well established. However, the use of serum markers has not yet been widely adopted by the medical community in breast cancer management (Table 1).

A biochemical measurement represents the summation of 'all' tumour bulk (or 'all micrometastases') in the body, while a measurable change in the size of 'a' disease (or 'a single metastasis') needs to be substantial before it can be noticeable clinically and/or radiologically. Serum markers therefore have the advantage of showing up the disease process (either response or progression) much earlier. While a measurable 'tumour' may represent either a viable or a necrotic tumour or both (e.g. after chemotherapy), biochemical measurement of serum marker levels indicates the 'biological' rather than the 'structural' behaviour of the tumour, making them more tantalising for guiding therapy in the advanced setting and, if they are at significant levels, the only way of assessing response in the adjuvant situation.

The currently available antigen-based serum markers are not sensitive enough to be used for screening and early diagnosis of primary breast cancer since the tumour burden is small in these circumstances. Intensive laboratory research is being carried out to extend the use of serum markers into these difficult areas. This may allow intervention at an earlier stage of cancer growth than awaiting a structural abnormality (as seen on a mammogram) to appear, which is the present situation.

The prognostic value of serum markers in breast cancer has remained uncertain; recent studies, including the paper in this issue by Gion and his colleagues, have shown that an increased level of CA15.3 is associated with poorer survival [1,2]. Gion has resolved the criticism on the independent prognostic value of serum markers by adjusting his results with all established prognostic factors. The other interesting finding in his study was the continuous nature of the prognostic relationship with increasing levels of CA15.3. While further studies are required to confirm his data, the results are promising. One day, we may be able to use serum marker levels to decide if a woman requires adjuvant systemic therapy. Employing markers would be more 'biological' than the present decision-making by 'statistical' risk calculation according to prognostic factors such as size, nodal status and histological grade. In this respect, the postoperative CA15.3 level may be more informative (to reflect the presence of 'micrometastases' after the primary tumour has been surgically removed) than the preoperative value as measured in these studies.

Although Kokko and colleagues (in this issue of the *EJC*) did not demonstrate a significant lead time when CA15.3 was measured regularly in the follow-up of 243 patients with primary breast cancer [3], previous large-scale studies from Spain and Germany involving over 9000 patients with primary breast cancer have shown the elevation of CA15.3 (54–56%), carcino-embryonic antigen (CEA) (46–53%) or either marker (54–81%) with a lead time of up to 6 months prior to clinical evidence of distant recurrence [4,5]. This is being further explored in an ongoing multicentre adjuvant endocrine therapy study (ATAC). Despite these findings, the

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Table 1
Roles of serum markers in breast cancer management

Roles	Evidence available	Clinically practised
Screening and diagnosis of primary disease	No	No
Prognostic value	Equivocal	No
Monitoring of primary disease	Yes	No
Diagnosis of metastatic disease	Yes	Becoming popular
Monitoring of metastatic disease	Yes	Becoming popular

medical community has been reluctant to use serum markers in the follow-up of primary breast cancer, whilst some oncologists are still carrying out regular bone and liver scans, which have not been shown to confer any survival benefit. Indeed, one of the reasons for not using serum markers to monitor these patients is because of the uncertainty of achieving a survival benefit from the early detection of metastatic spread. Two small studies have suggested such a benefit when earlier therapeutic intervention was instituted upon elevation of serum markers [6,7]. A larger prospective randomised study is required to confirm these findings.

Serum marker levels reflect tumour burden, and their roles in the diagnosis and monitoring of metastatic disease has been well established in our centre and others, both retrospectively and prospectively. In a multicentre study, 84% of patients had one or more of the three markers (CA15.3, CEA and ESR) significantly elevated before treatment of metastatic disease and the sensitivity rose to 96% during treatment [8]. Serum marker measurement is the only validated tool when the metastatic disease is unassessable by the International Union Against Cancer (UICC) criteria (e.g. sclerotic bone metastases and irradiated lesions). None the less, the oncology community has not widely adopted the use of markers as a standard method for the diagnosis and monitoring of treatment for metastatic breast cancer, despite the factual evidence and the potential advantages of biochemical over UICC assessment. We have previously shown that therapeutic intervention according to marker changes was associated with a better survival and quality of life [9]. Treatment can be targeted with earlier discontinuation of an ineffective treatment (and its resultant side-effects) and earlier commencement and possibly prolongation of an effective treatment.

While larger studies may be required to substantiate these advantages, the picture is clear enough to state that the use of serum markers should form part of the management of breast cancer in this era in which objective measurement has come to replace subjective judgement. Change of systemic therapy should certainly be made in cases of unassessable disease when serum markers are raised along with increasing symptoms and should be considered in all cases showing a serial rise, even without a change in symptoms [10]. To enable this, measurement of serum markers (at least with a MUC1 mucin and CEA) should be routinely carried at the time of diagnosis of metastatic disease, subsequently at regular intervals to monitor the response to systemic therapy, and at the change of therapy.

Whilst the aforementioned established roles of widely accepted serum markers (MUC1 mucin and CEA) need to be put into standard clinical practice, other markers may be of use in specific settings (e.g. serum measurement of extracellular domain of c-*erb*B2 for monitoring trastuzumab (Herceptin) treatment and measurement of bone metabolism for monitoring the treatment of bone metastases).

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