EUROPEAN JOURNAL OF CANCER 46 (2010) 1946–1948

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Editorial Comment

Towards a renaissance of subgross breast morphology

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ARTICLE INFO

Article history:
Received 19 March 2010
Accepted 22 March 2010
Available online 21 April 2010

Classical whole organ studies demonstrated long ago that 'extensive neoplastic transformation of the epithelium and multiplicity of the invasive sites' are frequent in breast carcinomas.[1] Almost three decades ago, Egan evidenced a clear difference in breast cancer-related mortality for patients with unicentric disease (2.5% per year) versus patients with multiple tumour foci (15% per year).[2] The few subsequent studies that used methods comparable to Egan's whole organ sectioning method confirmed that in up to 60% of breast carcinoma cases, the growth pattern was not unifocal.[3] Similar results have been obtained with the routine diagnostic use of large-format histological sections.[4,5]

Growing evidence suggests that there are genetic alterations in morphologically normal breast tissue that are similar or identical to the genetic alterations in cancer cells.[6] We formulated the theory of the sick lobe, positing that these alterations are a characteristic of a breast lobe with an increased stem cell/progenitor cell burden within which breast cancer develops, often at multiple sites.[7] Modern radiology, especially magnetic resonance imaging, often detects multiple malignant lesions within the same breast and these lesions frequently show lobar ('segmental') distribution.

Thus, the theoretical background as well as the genetic, molecular, radiological and morphological evidence indicates that breast carcinomas are not a unifocal process in the majority of cases. It is obvious that the tumour shown in Fig. 1 cannot be properly characterised using a single parameter, i.e. tumour size (the largest dimension of the largest invasive focus, marked with double arrow in the image), as recommended by international staging systems. Instead, the distribution of the lesions (i.e. multifocal) and the extent of the disease (the area or tissue volume including all malignant lesions) should also be described, as should the morphological heterogeneity, between and within tumour foci, if evident.

This raises the question of why international guidelines do not recommend such detailed characterisation of the subgross morphology of breast cancer. One reason may be that a specially adapted large-format histopathology technique is required for this complex task; the conventional fragmenting small-block technique used in most breast pathology laboratories today is insufficient. Another reason is that the large-format slides themselves are not enough: the images on the large-format slides must be systemically correlated with radiological findings, especially with ultrasound and magnetic resonance images. Third, the community of breast cancer researchers as a whole has shifted away from the analysis of complex subgross breast morphology and towards analysis of the more easily detectable and accessible dominant invasive tumour focus, which represents an inexhaustible source of molecules and genes to study. Current efforts focused on finding predictive molecular markers and blocking agents that will 'cure' the malady regularly disregard the complexity of breast cancer morphology and the multiplicity and heterogeneity of the tumour foci. Lastly, the few published studies to examine the influence of multifocality on prognosis failed to demonstrate a significant effect on overall survival, although

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.03.023

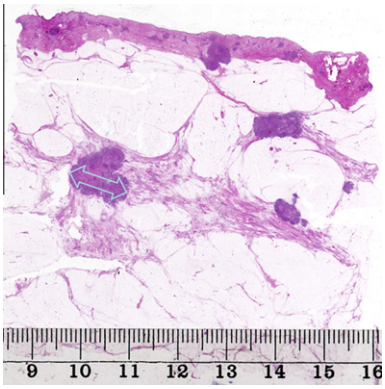

Fig. 1 – Large-section histopathology image of a multifocal invasive breast carcinoma. The largest dimension of the largest invasive focus is marked with a double arrow.

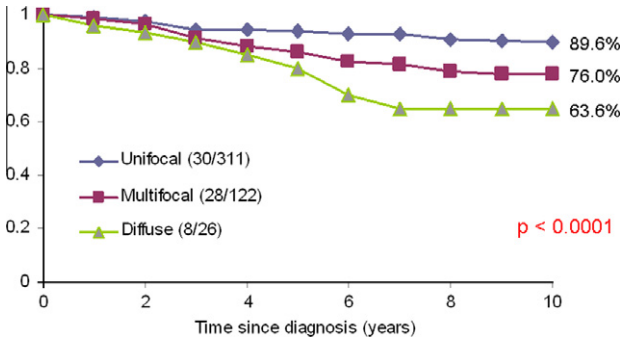

Fig. 2 – Cumulative breast cancer specific survival in a consecutive series of invasive breast carcinoma cases 15 mm or larger documented in large-format histopathology slides by distribution of the invasive component (Dalarna, Sweden, 1996–1998).

these studies regularly showed that multifocal cases had increased lymph node positivity rates,[4,5,8,9] and some studies showed that multifocality correlated with shortened disease-free survival.[8]

Five years ago Coombs and Boyages posed an important question: 'Multifocal and multicentric breast cancer: Does each focus matter?'[9] In this issue of *European Journal of Cancer*, the same authors, together with Dr. Jayasinghe, provide the answer: 'Multifocal breast cancer and survival: Each focus does matter, particularly for larger tumours.'[10] In contrast to previous studies on multifocality and survival, the authors demonstrate statistically significant differences in 10-year survival between unifocal and multifocal cases involving tumours larger than 20 mm, provided that the single dominant tumour size per case was compared. The difference in survival disappeared when the tumours were classified according to their aggregate tumour size. The authors focused on invasive foci and did not analyse the influence of the in situ component. The low proportion of multifocal cases in their series, 11%, indicates histotechnical limitations and is similar to the proportion in other published series based on clinical, radiological or macroscopic findings. The authors did not consider diffusely growing invasive carcinomas in this article, although this growth pattern is associated with the lowest cumulative breast cancer specific survival (Fig. 2). Thus there is an opportunity for refining these observations. Future studies can take advantages of both modern radiology and large-format histopathology, since a detailed correlative approach shows about 35% multifocality of the invasive component and >60% non-unifocal distribution of the lesions if the distribution of the invasive component is combined with that of in situ lesions.[4] Nevertheless, the message of Boyages et al. is clear: Aggregate tumour size, i.e. the sum of the largest diameters of the invasive foci, correlates better with long term overall survival and should be used for multifocal cancers instead of the single largest dominant tumour diameter, which is currently recommended.

This publication is important. It directs our focus back to subgross morphology and indicates that multifocality is a powerful morphological prognostic parameter in breast cancer. There is still much to do: there is a clear need for internationally accepted definitions, for determining the preferred assessment methods, defining the role of preoperative imaging, determining the indications for treatment modifications, and so on. We also need to assess the influence of multifocality on prognosis for <20 mm cancers. Nevertheless, we face a new era: an era of multimodal radiology; an era in which clinicians are more and more open to modifying therapeutic decisions for multifocal lesions; an era in which the TNM7 allows for the possibility of multifocality within the same quadrant; an era in which the follow-up times for correctly diagnosed multifocal breast carcinomas are sufficiently long to provide important outcome information; an era in which an internationally highly ranked oncology journal opens the door to publication of these results. This new era is one marked by change and innovation. We hope that a renaissance of subgross morphology is on the way, and that lesion distribution and disease extent will become accepted prognostic breast cancer parameters with clinical importance equal to dominant tumour size in the near future.

Conflict of interest statement

None declared.

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