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Functional Maps of Metastases from Breast Cancers: Proof of the Principle that Multidimensional Scaling Can Summarize Disease Progression

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Abstract. The mathematic technique of multidimensional scaling can create "functional maps" of metastases from breast cancer such that positions of organs in these maps are proportional to the probability of metastases. Areas that are likely to share disease are close together in a functional map, even though they may be physically distant, and vice versa. Two functional maps of breast cancers—one of local metastases to axillary levels I to III and another of distant metastases—are statistically significant and clinically meaningful. The maps accurately reflect the clinical data ($r > 0.97$, $p < 0.01$), and so the progression of disease is revealed in simple visual summaries. As an analogy, the metastatic sites are like buoys on a fluid surface, and cancer spreads from a primary tumor like waves emanating from a point of impact on that surface. Metastases are predicted when the waves swamp the buoys. Because breast cancers do not always spread to the next nearest site, these functional maps do not resemble anatomic maps. The maps are a view of the body as "seen" by the tumor. Several well known clinical features are seen in these maps: most local metastases are to axillary level I; upper-inner primaries spread equally to levels II and III; in-transit metastases in the lymph and blood vessels do not follow the pattern of other distant metastases. Future functional maps can expand these summary diagrams to include biologic parameters (gene-expression profiles or endocrine response) and give valuable insights into patterns of recurrence in different populations.

"The ultimate event that leads to the mortality of breast cancer is metastasis" [1]. Knowledge of the likelihood of metastases is important for staging and planning treatment for patients with breast cancer [2]. The cellular changes that lead to metastases have been well studied [3], but difficult questions remain about the pattern of metastasis [4–6].

Various authors have debated the relative probability of metastases in different populations of patients [7, 8] and have reported their findings in different ways [5, 9–11]. Underlying trends can be difficult to compare when the data are described in text form or are presented in complex tables. A simple, graphic, universally applicable method for displaying patterns of metastases would help summarize and compare data from around the world.

Using multidimensional scaling (MDS) it is possible to create what we call "functional maps" of the body such that distances in the map represent probabilities of metastatic spread [12]. Sites that are equally likely to share metastases are close together in such a map, even though they may be physically distant. Conversely, sites that have different probabilities of metastases are far apart in a functional map, even though they may be physically adjacent. Thus a functional map may bear little resemblance to an anatomic map. For example, if the brain and liver had similar probabilities of metastases, these regions would be close together in a functional map.

If a disease, such as basal cell carcinoma of the skin, were to spread simply to the next nearest area, the functional map would resemble a map of the local anatomy. Treatment in such a situation is relatively easy: Expand the area of resection from the primary tumor until the margins are clear and then stop. Of course, breast cancer does not behave in this manner. The disease spreads and recurs in complex patterns, usually not in tissue immediately adjacent to the primary tumor. Therefore we ask a computer to redraw relevant areas of the body into a space of the computers devising such that the disease does spread to the next nearest area—within a mathematically defined landscape. Patterns of progression are then easily seen in a map that represents this result.

The goal of this article is to show that functional maps can be constructed from data on breast cancer metastases. This is demonstrated twice: with clinical data on local metastases and distant metastases. These maps are both statistically significant and clinically meaningful. This proves the principle that complex patterns for clinical data can be objectively summarized in simple pictures—the output of multidimensional scaling. The functional map is a succinct depiction of tumors' behavior. Future maps can thus depict the divergent behaviors of tumors that differ in endocrine response or gene expression, for example.

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Table 1. Frequency of metastases to the axilla.

Site of metastasis	Frequency, by location of primary tumor					
	Upper outer	Lower outer	Upper inner	Lower inner	Central	Total
Level I	64	9	25	5	22	125
Level II	53	8	15	4	23	103
Level III	24	2	10	2	7	45
Total metastases	141	19	50	11	52	273
Total cases	75	11	28	6	30	150

Table 2. Frequency of metastases to eight sites.

Site of metastasis	Frequency, by location of primary tumor				
	Upper outer	Lower outer	Upper inner	Lower inner	Total
Axilla	83	26	16	11	136
Lymph vessels	64	14	10	8	96
Blood vessels	44	12	9	5	70
Skin	17	3	1	2	23
Bone	12	2	1	0	15
Lung	11	1	0	2	14
Liver	9	2	0	1	12
Supraclavicular node	6	2	2	1	11
Total metastases	246	62	39	30	377
Total cases	200	59	53	31	343

Materials and Methods

Map 1: Regional Metastases

Data from 150 sequential cases of female breast cancer with axillary metastases from the Tata Memorial Cancer Center in India between October 1989 and February 1998 were analyzed. The patients ranged in age from 27 to 76 years (mean ± SD, 50 ± 11 years). Pathology reports indicated which of three levels of axillary lymph nodes contained metastases. Nodes of level I are lateral to the pectoralis minor muscle, level II is below the muscle, and level III is medial to the muscle [13]. Primary tumors were sorted into five locations: upper, lower, inner, and outer quadrants, and a central area underneath the areola. Table 1 shows the frequency of metastases to each of these areas. All metastases were recorded at the initial surgery.

The raw data were matrices of 1's and 0's: 1 meaning the presence and 0 the absence of metastases. There was one matrix for each primary site. Columns of the matrix were possible metastatic sites (axillary levels I, II, and III), and rows were cases. Binary euclidean distances were used to calculate functional distances between all possible pairs of metastatic sites. The binary euclidean distance is the square root of the number of times one site is positive and the other is negative. If the patterns of disease were identical in all cases (either 1's at both sites or 0's at both), the distance would be 0. Conversely, this measure of distance would reach a maximum of the square root of the number of cases if the presence of metastases at two sites were different in every patient. These calculations were repeated separately for each pair of sites for each primary location.

These distance measures (three pairs of three sites times five primaries) were subjected to multidimensional scaling (MDS) [14, 15]. MDS creates a functional map of the metastatic sites, positioning points such that their coordinates match the input data. Locations of the primaries are then found by iterative search, such that when a metastasizing cancer is modeled as an expanding ellipse in the functional map, distances to the secondary sites are maximally correlated with the probabilities of metastases [16].

With MDS, underlying trends in the input data are depicted as a picture or map. MDS also calculates a measure of how well that best-fitting map coincides with the input data. The measure of goodness-of-fit is used to establish the statistical significance of the result. Because there are no tabulated statistical tests to evaluate the significance of an MDS result, we used the neutral model or Monte Carlo method, an assumption-free but labor-intensive approach that is always appropriate. We repeated the analysis with random data. We created matrices of random 1's and 0's, matching the percentage of positive nodes and the average number of cases per primary to that in the real data. We calculated binary euclidean distances, and for each set of random data we let MDS find the functional map that best fit those distances and recorded the goodness-of-fit. We did this 100 times and determined that the goodness-of-fit to the real data was greater than all fits to random data, thereby establishing statistical significance at the 0.01 level or better.

Map 2: Distant Metastases

Metastases to distant sites were analyzed using data from 343 cases of unilateral female breast cancer treated at the Aga Khan University Hospital in Pakistan between 1988 and 1996. The women ranged in age from 22 to 88 years (mean ± SD, 48 ± 13 years).

Eight areas to which the cancer could spread were mapped: skin and nipple, vessel invasion, lymphatic invasion, axilla, supraclavicular node, lung, bone, and liver. Metastases were assessed in the axilla by biopsy or fine-needle aspiration (FNA), in the supraclavicular node by FNA, in the lung by FNA when accessible or by imaging, in the liver by computed tomography or ultrasonographic imaging, and in the skin by biopsy. Lymphatic and vessel invasions were detected in the histologic specimen. Metastases were recorded at the time of presentation or initial treatment. Table 2 shows the frequency of metastases to each of these areas. A total of 112 euclidean distances (28 pairs of eight sites times four quadrants) were calculated from the raw data and subjected to MDS. All other procedures were the same as described above.

Results

Map 1

Figure 1A shows the map of axillary levels from cancers in the lower outer quadrant. Circles show the functional position of this primary site. Diamonds show the functional locations of axillary levels I to III. Distances between points in the map match the input data as closely as possible. The probability of metastases can be modeled as an expanding circle in this functional map. Axillary levels that are functionally closer to the primary lesion are more likely to be pathologically positive for metastases. We see that most metastases are expected at level I because that site is closest to the primary lesion in the functional map. A slightly smaller number of metastases are expected at level II, and few metastases are expected to level III because this is functionally most distant. These trends can be

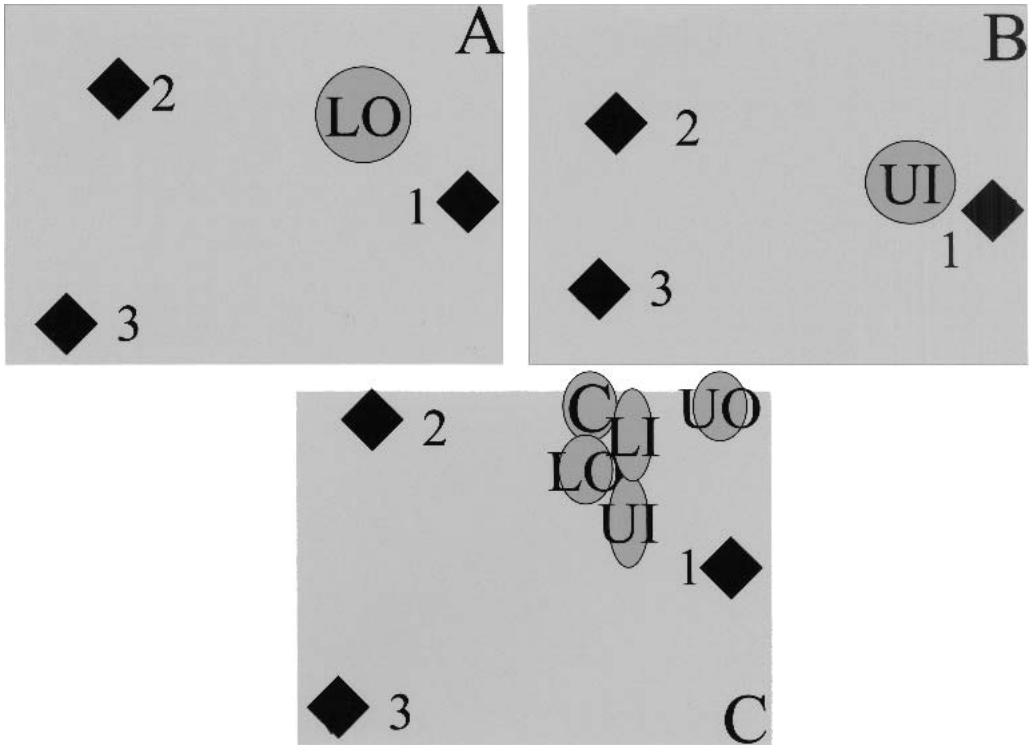

Fig. 1. Functional map of axillary metastases. **A.** Patterns of metastases from the lower outer quadrant. Three diamonds represent axillary levels I to III ipsilateral to the primary. A circle represents the primary lesion. Distances from the primary lesion to axillary levels represent the frequency of the metastases. Most of the metastases from these primaries go to levels I and II. **B.** Metastases from the upper inner quadrant. A more nearly equal number of metastases go to levels II and III from this primary lesion. **C.** Combined functional map of five primary tumor locations. The patterns of metastases from each primary are now represented as ellipses, with major axes in different directions. This functional map explains 99% of the data from 150 patients, the result being statistically significant ($p < 0.05$). LO: lower outer; UI: upper inner; C: central; LI: lower inner; UO: upper outer.

confirmed by the summary data in Table 1. Maps from the central and upper outer primaries are similar.

Figure 1B shows the map for primaries in the upper inner quadrant. Levels II and III are closer together than in Figure 1A, suggesting a more balanced number of metastases to levels II and III from upper inner primaries, a trend that can be confirmed by the raw data in Table 1. The map for the lower inner quadrant is similar.

The functional distances in these maps are closely correlated ($r > 0.999$) with the raw data in Table 1 ($p < 0.01$). Hence, these simple geometric models summarize more than 99% of the data from 150 cases of metastatic breast cancer. A single, combined functional map of all primaries would be an even more succinct summary of the data. Such a unified depiction of metastases from all primary locations is seen in Figure 1C.

To understand the map of multiple primaries, note first that the axillary levels in Figure 1A, B are stretched slightly differently. In Figure 1B, levels II and III are closer to each other than in Figure 1A. It is as valid to depict metastases as circles expanding into configurations of axillary levels that are stretched differently for each primary as it is to depict metastases as ellipses expanding into a single configuration of axillary levels that best fits all the data. That is, stretching either the circle or the axillary levels results in the same predictions. A stretched circle is an ellipse. Suppose, for example, we stretched Figure 1B vertically until the axillary levels could be superimposed on those in Figure 1A. The circle in Figure 1B would become a vertically slender oval. Given input data from multiple primaries, MDS performs an operation similar to this stretching to fit the data from each primary to a single best-fitting configuration of axillary levels.

Figure 1C shows the functional map of axillary levels for all five primary locations. The lower primaries (both inner and outer) expand as horizontally elongated ellipses. The other three primaries expand as a circle in this map. The fit of this functional map to all the input data is statistically significant ($p < 0.05$). Figure 1C explains 99% of the variance in the input data. Results from 100 iterations of a neutral model (explained above) showed that the correlation in the real data (0.996) was greater than 95 of the correlations in 100 repetitions with random data, so we know the result is statistically significant at the 0.05 level.

We must look at the positions of the axillary levels to interpret the dimensions in this map. By convention, the horizontal dimension explains most of the data. This is a numerical ordering of the levels, with II closer to III than I. This fits with the overall probability of metastases to the three levels of the axilla ($r = 0.8$). The second, or vertical, dimension separates the inner primaries (which are stretched along this dimension) from the outer and central primaries.

Map 2

Figure 2 shows the functional map of distant sites in a manner identical to that in Figure 1 for local metastases. Figure 2A shows metastases from the lower outer quadrant, and Figure 2B shows the map from the lower inner quadrant. These maps fit the data well ($r > 0.96$). As in Figure 1A, B, these secondary sites in Figure 2A, B are stretched differently. Figure 2C was constructed as a single map for all four quadrants by stretching the circles into ellipses, as already described. The fit of this functional map to the input data is statistically significant ($p < 0.01$). The point-to-point distances in Figure 2C are highly correlated with the distances derived from the clinical data ($r = 0.97$). This means that Figure 2C explains 93% (r^2) of the variance in the input data. Results from 100 iterations of a neutral model showed that the greatest correlation obtained with random data was 0.66. The correlation in the real data ($r = 0.97$) was greater than all correlations in 100 repetitions with random

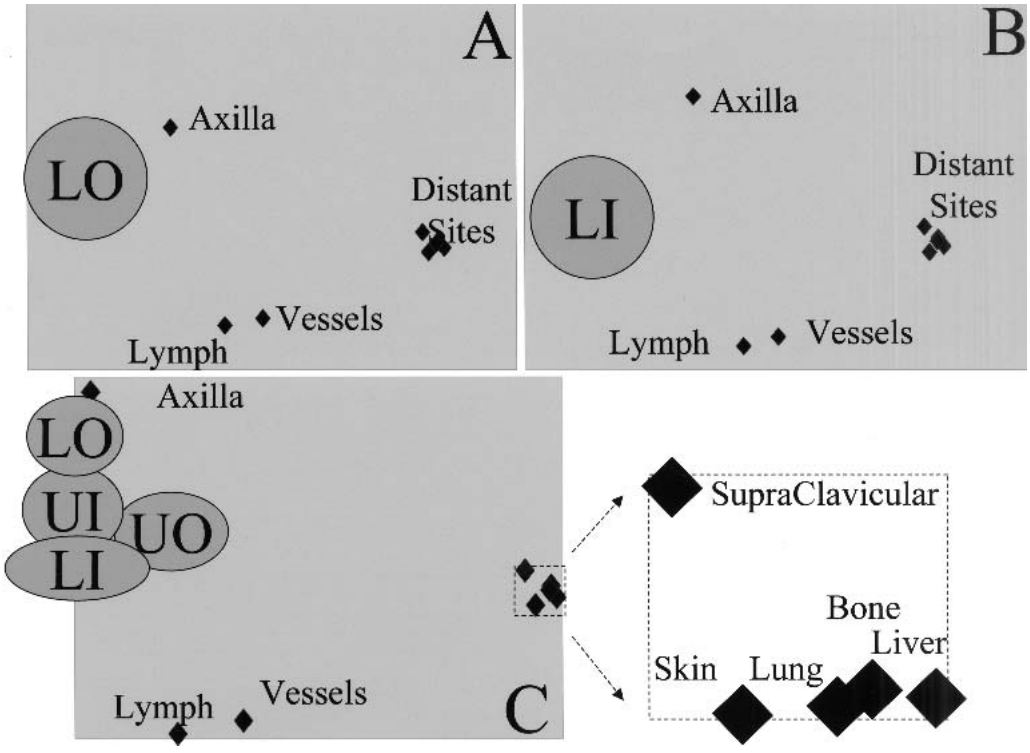

Fig. 2. Functional map of distant sites. **A, B.** Functional maps from different primary lesions with slightly different patterns of spread. **C.** Combined map for all quadrants. **Inset.** Functional locations of five distant sites.

data, so the result is statistically significant at the 0.01 level or better.

Discussion

Map 1

Multidimensional scaling successfully summarizes 150 cases with axillary metastases in a simple picture. There are several conclusions from this analysis that fit clinical expectations. First, the extent of spread along a second dimension in the map shows that patterns of metastases from the inner quadrants are different from those of the outer and central locations. This separation of inner and outer quadrants fits known patterns of metastases [17]. Outer quadrants spread to axillary levels in numeric order. A more equal number of metastases from inner primaries (especially the upper –inner ones) go to levels II and III. Second, because the functional map is two-dimensional,[1] we know that not all axillary metastases follow a simple progression from level I to II to level III. This can be confirmed by examining the raw data. Altogether, 28 cases (19%) had "skip" metastases (i.e., positive nodes in level II or III without a positive node at a lower level). Others have reported similar probabilities of skip metastases [18, 19].

Map 2

The axilla is separated from distant sites along the most important (horizontal) dimension of the functional map and separated from the lymph and blood vessels along the secondary (vertical) dimension. The horizontal position of sites in Figure 2C is similar to the overall frequency of metastases in Table 2 ($r = 0.99$). The axilla is a uniquely important region when evaluating metastatic disease [2, 20]. The position of the axilla in Figure 2 agrees with clinical intuition that spread to regional (axilla) versus distant sites (lung, liver, bone) is of paramount importance when evaluating this disease. The second dimension separates lymph and blood vessels from the other sites. This axis is unrelated to the overall frequency of metastases ($r = 0.19, p = 0.65$). Lymphatics surrounding a primary tumor do not always show involvement [21]. Thus metastasis does not occur via a simple process of permeation to the next nearest site [2], an interpretation consistent with this two-dimensional functional map.[1] Tumors in the lower inner quadrant are most likely to be caught in transit in the blood and lymph vessels of the breast before they arrive at the axilla, and these in-transit malignancies do not follow the same pattern as other local and distant metastases. In summary, Figure 2 quantifies clinical impressions that patterns of spread depend on the quadrant of the primary lesion and whether the metastases are local, distant, or in transit [20].

General Comments

Multidimensional scaling is a data-reduction technique. We use the term "functional map" to refer to the MDS output from data regarding the presence or absence of metastastic disease in various locations. Functional maps are succinct visual summaries of data that are usually presented in text or tables. The maps are transfor-

[1]Guidelines for determining the appropriate number of dimensions in an MDS analysis are to look for the last large increase in goodness-of-fit as dimensions increase. Fit always increases with the number of dimensions, but if the increase is small the added dimension is probably not important. Dimensions in the functional map should be interpretable, and it is desirable if the dimensions are uncorrelated. All these criteria suggest that these functional maps should be two-dimensional.

mations of such data into diagrams, where important trends are easier to identify and appreciate. A strong signal is extracted from background noise. Consistent with the goals of modern medical informatics, this automated technique can identify the important underlying patterns in large or small amounts of variable data.

This study demonstrates that statistically significant functional maps can be created from clinical data on metastases from breast cancer. Map 1 is a "fine-grained" analysis, showing that MDS is appropriate for detailed records of local metastases. Map 2 is a more "coarse-grained" analysis, showing that MDS is appropriate for organ-level summaries of metastases. A combined summary of local and distant metastases is possible with an MDS analysis of data where both axillary levels and distant metastases are recorded in the same patients.

Interactive visualizations of predicted metastases can be made from functional maps [16]. Predicted metastases can be viewed with any Java-enabled Internet browser at http://www.uth.tmc.edu/oto. Select "Breast Cancer Visualization" under the "Research" heading toward the bottom of the home page. Select the primary location (quadrant) from the menu on the left. Move the slider on the right to indicate how far you think the disease might have spread. The program displays predicted metastases as changing colors on a realistic image of the body. Such visualizations can be useful for educating both patients and health-care workers. Select the "Abstract Map" tab at the top of the screen and repeat the selection of primary sites and extent of disease. The expanding ellipses show how this model predicts disease.

As an analogy, it is as if the possible sites of metastasis were arranged like small buoys on a fluid surface. The primary malignancy is like the glancing impact of a bullet on that surface. The resulting waves have a starting location and a tendency to spread more in one direction than another. Recurrence is predicted when the spreading waves tip particular buoys. MDS solves the problem of finding the coordinates of the buoys, the impact sites, and the shapes of the waves, such that the predictions are in maximal agreement with the input data. The result is similar to a wartime map of enemy supply lines. The prevalent shipping lanes (malignant potential) are represented by proximity to the source.

Patterns in different countries [7] or different populations can be easily compared. Thus functional mapping provides a method for comparing patterns of surgically treated diseases around the world. A functional map can confirm expected trends and suggest new ways of looking at the data. The present data are unique in that the patients in South Asia often present with advanced disease, and follow-up is often poor. Maps of disease in more developed countries are different [22]. Functional maps provide a way for surgeons in developing countries to see how patterns of local disease might be different from those in other countries.

Other analyses [12, 16, 23, 24] have made functional maps from metastases of head and neck cancers to regional lymph nodes. A comparison of metastatic patterns from different diseases using functional maps could form the basis of theories about malignancies arising in various organs of the body.

Future analyses will improve these maps. For example, internal mammary nodes could be added to a functional map to help evaluate the importance of this staging criterion [25, 26]. We could divide cases by the age of the patient [19], the histology of the primary [10, 22], or the estrogen receptor status [22, 27] and use functional maps to display differences in patterns of metastases caused by these important factors. With the advent of modern molecular analyses, breast cancers can be divided by patterns of gene expression or protein production [8, 27] into subsets that differ in terms of the probability of metastases and recurrence [28].

An important reason to use MDS to analyze clinical data is that the same technique is now being used to analyze genetic differences in this disease. Recently, MDS has been used to uncover underlying trends from the microarray analyses of thousands of genes [8, 29–33]. It has also been used to describe the effectiveness of anticancer drugs [34] and life-style decisions that increase the risk of cancer [35]. Functional mapping can relate the phenotype to the genotype of this disease through easily interpretable maps.

Résumé. La technique mathématique d'étalonnage multidimensionnel peut créer une «cartographie fonctionnelle» des métastases à partir du cancer du sein; la position des organes visionnés dans cette cartographie est proportionnelle à la probabilité de métastases. Les régions susceptibles de porter des lésions sont proches les unes des autres sur une carte fonctionnelle, même si elles sont physiquement distinctes et vice versa. Ces deux types de cartes fonctionnelles de cancers du sein—une des métastases locales aux niveaux axillaire I–III, et une autre des métastases à distance—sont statistiquement et cliniquement significatifs. Les cartes reflètent avec précision les données cliniques ($r > 0.97$, $p < 0.01$), et ainsi peut-on analyser la progression de la maladie par des RéSUMés visuels simples. Par analogie, on peut considérer les sites métastatiques comme des bouées sur une surface liquidienne, et le cancer s'étend à partir de la tumeur primitive comme des vagues partant d'un point d'impacte sur cette surface. On peut prédire les métastases lorsque les vagues envahissent les bouées. Puisque les cancers du sein ne se métastasent pas toujours au site le plus proche, ces cartographies fonctionnelles ne ressemblent pas à des cartographies anatomiques. Ces cartographies sont des vues du corps, «vu» par la tumeur. Plusieurs caractéristiques cliniques bien connus, peuvent être matérialisés par ces cartographies: la plupart des métastases locales sont au niveau I de l'aisselle; les tumeurs primitives du quadrant supéro interne se métastasent volontiers aux niveaux II et III; les métastases transitant par la lymphe et les vaisseaux sanguins ne suivent pas le chemin des autres métastases à distance. A l'avenir, on peut étendre ces cartographies fonctionnelles pour inclure des paramètres biologiques (profils d'expression génétique ou réponse endocrine) et donner des informations utiles en ce qui concerne les schémas de récidive dans des populations différentes.

Resumen. La técnica matemática de la escala multidimensional puede crear "mapas funcionales" de las metástasis del cáncer del seno, en tal forma que la posición de los órganos en estos mapas es proporcional a las probabilidades de las metástasis. Las áreas con probabilidad de compartir la enfermedad aparecen muy juntas en el mapa funcional, aunque estén físicamente distantes, y viceversa. Dos mapas funcionales del cáncer del seno—uno de las metástasis locales a los niveles axilares I-III, y otro de las metástasis distantes—son estadísticamente y clínicamente significativas. Los mapas reflejan con certeza los datos clínicos ($r > 0.97, p < 0.01$) y por lo tanto la progresión de la enfermedad se revela en sumarios visuales simples. Como analogía, los lugares de las metástasis son como boyas sobre una superficie líquida, y el cáncer se extiende a partir del tumor primario como ondas generadas, por un impacto sobre la superficie. Se pueden predecir las metástasis cuando sobrepasan las boyas. Puesto que los cánceres mamarios no siempre se extienden al lugar más próximo, los mapas funcionales no asemejan mapas anatómicos. Estos mapas son más bien como una visión del cuerpo como "lo ve" el tumor. Diversas características clínicas bien conocidas pueden ser visualizadas en estos mapas: la mayoría de las metástasis se desarrolla en el nivel axilar I; los primarios superiores e interiores se extienden por igual a los niveles II y III; las metástasis en tránsito en los vasos linfáticos y sanguíneos no siguen el patrón de otras metástasis distantes. Mapas funcionales futuros pueden ampliar estos diagramas sumarios para incluir los parámetros biológicos (perfiles de expresión génica o respuesta endocrina) y proveer valiosa información sobre los patrones de recurrencia en las diferentes poblaciones.

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