SEMINARS IN BREAST DISEASE

Problems in the Assessment of Tumor Size: An Elusive Grail in Current Practice

Michael D. Lagios, MD

Tumor size, the most significant prognostic feature for distant disease-free survival among image-detected T1N0 breast carcinomas, is often improperly determined. Such miscalculations can result in a recording of a larger T-size and stage, and inappropriate recommendations for adjuvant therapies. Common errors in tumor size determination are reviewed and illustrated.
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Specialization within the broad field of Breast Oncology is a pervasive and rapidly accelerating process. Newer technologies, in particular, have permitted more reliable early detection, definitive percutaneous biopsy, and more effective and less morbid surgical and radiotherapeutic options. Yet, despite these many innovative advances, almost all therapy is based on hematoxylin and eosin-stained sections, a technology now more than a century old, and the identification of a few prognostic factors: nodal status, grade, size, and margins. Prognostication based on gene signature (microarray analysis) holds tantalizing promise, but awaits a rigorous comparison with conventional prognostic features, and was validated using data which primarily derived from older women with larger clinical tumor size.[1] This discussion will focus on what is considered the most straightforward, but in fact on review the least reliable of the conventional prognostic factors: *tumor size*.

A growing majority of newly detected invasive breast cancers are clinically occult, and detected by imaging alone. The mean size of such image-detected carcinomas is 11 mm, and 90% will be node negative. Imaging technologies, particularly mammography, have clearly reduced the size, the frequency of nodal involvement, and to some extent the grade of invasive breast cancer,[2,3] and there is some evidence that distant disease free survival is improved in those detected by mammography.[4,5]

For these T1, N0 image-detected carcinomas, the most important prognostic feature for distant disease-free survival is *tumor size*, which often receives the least attention in terms of definition. Defining the Scarff-Bloom-Richardson score and biomarkers such as estrogen and progesterone receptor, HER-2/neu by immunohistochemistry or FISH and K_i-67 (MIB-1), and more recently gene signature analysis all receive more attention, time, and resources. Tumor size is also an important prognostic feature for duct carcinoma in situ (DCIS), as exemplified by outcome data,[6] and as utilized in the Van Nuys Prognostic Index, but only rarely is tumor size properly calculated or correlated with imaging studies.

In a detailed synoptic report of an invasive carcinoma, there is often no documentation of how tumor size was established, yet patient care is often predicated on the synoptic record alone. Tumor size can be determined in several ways (Table 1), and all are subject to some error.

Clinical palpation is recognized as the least precise method of size determination, and results both in over and underestimation of size. Despite this shortcoming, a number of randomized trials and derivative studies are entirely dependent on clinical size, as determined by the palpating finger.[1,7] Palpation cannot distinguish invasive and noninvasive disease, therefore, clinical estimates often include in situ components. Only the size of the invasive carcinoma has prognostic significance for distant disease-free survival and cause-specific survival.

The most prevalent pathologic method is to measure the maximum gross size of the invasive tumor (the prognostic size), on the basis of the wet tissue. However, what intuitively should be a simple measurement is often in error, for several reasons.

The Breast Cancer Consultation Service, Tiburon, CA.
Address reprint requests to Dr. Michael D. Lagios, The Breast Cancer Consultation Service, 11 Benton Court, Tiburon, CA 94920. E-mail: MLAGIOS@aol.com

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Table 1 Methods of Tumor Sizing

- Clinical assessment
- Imaging analysis
- Gross pathology estimate
- Microscopic measurements
- Pathology–imaging correlation

Table 3 Potential Errors in Gross Tumor Size Determination

- Inclusion of in situ and/or benign disease and post-biopsy reactions in measurement
- Tumor sectioned on its short axis minimizing tumor size
- Underestimated tumor size: non-palpable or grossly invisible disease

Tumor Registrar Errors

In many hospitals, a tumor registrar will immortalize tumor size by recording and tabulating this important feature from the available pathology report. In the absence of a given tumor size, the size of the biopsy is not infrequently recorded in default as the actual tumor size. When this occurs, it results in erroneous tumor registry reports as well as inaccurate quality assurance activities—both of which are intended to provide appropriate feedback to clinicians to improve patient care.

Eyeball Estimate

If the tumor sizes as recorded in the hospital tumor registry are tabulated, one will find that there is a clustering around 10, 15, 20, and 25 mm. Only 20% of the numbers 1 to 100 should be evenly divided by 5, yet in our own hospital data from 1993 (Table 2), 60% of all recorded tumor sizes could be evenly divided by 5. Clearly, many of these sizes were estimated pathologically. Although a disposable plastic metric ruler may be the least expensive instrument employed in pathology practice, it is useless if no attempt is made to apply the ruler to the specimen.

A gross measurement can be unreliable, even when a ruler is employed (Table 3), since this measurement may include adjacent areas of noninvasive carcinoma, proliferative breast disease or even reaction from a prior biopsy. This error results in increasing the prognostic tumor size, and may result in patients being over-treated.

Sectioning Errors

A second area in which gross tumor size can be misrepresented results from the common practice of pathologist sectioning (ie, "bread loafing") a resection at right angles to its long axis (Fig. 1). Particularly when this is done without knowledge of the size(s) established by preoperative imaging, or when the pathologist fails to calculate the size based on a sequential series of sections containing the tumor, a much smaller prognostic size can be recorded. This result also impacts treatment decision making.

Table 2 Frequency of Estimated Tumor Size*

Year	1992	1993	1994	1995
N	63	38	55	70
Percent divisible by 5	60	54	51	28

*20% of tumor sizes from 1 to 100 mm can be evenly divided by the number 5, eg, 5, 10, 15, 20 mm. Percentages greater than 20% likely reflect "rounding off" estimates of tumor size not measurements.

Addition Errors

A third error in determining gross or microscopic tumor size results from summing the sizes of the carcinoma in multiple separate morcellated fragments of a resection, or in the multiple separate fragments of a core biopsy procedure. The American Joint Commission on Cancer Staging Manual Sixth Edition[8] prohibits this type of calculation, which results in much larger prognostic sizes (Fig. 2). Using the same logic would result in a small sliced crabapple expanding into a cantaloupe.

For the majority of image-detected invasive breast cancers, these errors in over or underestimating tumor size are made possible either because of ignorance or indifference to preoperative imaging studies. Such correlation is required to confirm an adequate excision and tumor size, particularly for small image-detected lesions.[9,10] It is difficult to cite a 40-mm tumor size when the pathologist is aware of the fact that the preoperative mammogram and ultrasound only established a 16-mm carcinoma.

There are situations when a definitive resection for a previously biopsied small T1 carcinoma reveals either no residual disease, or only microscopic tumor. In these circumstances, the maximum extent of the invasive component in the prior core biopsy material should be correlated with the preoperative imaging to establish the most accurate estimate of tumor size.

Two actual examples of miscalculated tumor size will illustrate the point: A 46-year-old developed an interval spiculated mammographic density in the left breast, and underwent a needle localized excisional biopsy. The surgeon morcellated the specimen into six fragments, each of which was separately inked by the pathologist. The pathologist estimated a large T2 or T3 size, based on adding the sizes or extents of invasive duct carcinoma in the largest of the two fragments (some 4.5 cm), or all four of the involved fragments (7.3 cm). Oblivious to the implications of a morcellated specimen, he noted multiple margins were transected (Tables 4 and 5; and Fig. 3). The patient was presented to a prospective tumor board, which concluded that induction chemotherapy would be most advantageous before mastectomy. The mastectomy specimen revealed only a small post excisional scar, and no evidence of tumor involution. Review of the preoperative imaging at that point documented a T1c-sized carcinoma in both mammographic and ultrasound studies (Figs. 4 and 5). At the very least, the patient underwent an unnecessary mastectomy, and probably a more rig-