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Letter to the Editor

Re: "Behjatnia B et al. "Does size matter? Comparison study between MRI, gross, and microscopic tumor sizes in breast cancer in lumpectomy specimens". Int J Clin Exp Pathol 2010;3(3):303-309".

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We read with great interest the article by Behajatnia et al [1] on assessing the gross dimensions of an invasive breast carcinoma. Given the prognostic significance of tumor size in breast cancers, the authors are to be commended for their attempt to bring a more evidenced-based approach to the determination of this important parameter. The authors report that gross measurement or MRI will underestimate or overestimate the tumor size in a substantial proportion of cases, with microscopic measurement as the "gold standard". It is on the latter – their methods of microscopic measurement of tumor – that we wish to offer some commentary. Three different microscopic methods were used to assess tumor size: (1) Tumor seen on one slide only was measured on the slide; (2) Tumor present on one slice only was measured using a one plane reconstruction model (adding tumor dimensions on microscopic sections); (3) When tumor involved multiple slices, size was calculated by multiplying the number of slices involved microscopically by the average thickness of the slice.

Method numbers 1 and 2 are more or less uniformly accepted as the best for the scenarios depicted. Method number 3 raises some questions, and in our opinion, is likely to overestimate tumor size. Most of the issues have to do with estimation of the thickness of the slice (on the basis of which calculations were made). How was the thickness of each slice determined? Was this calculated (longest dimension divided by number of slices) or was this measured for each slice by the prosector? It would be important to know how the slice thickness was determined, to establish the accuracy of calculations, since this method is used by the authors as the "gold standard" for the determination of tumor size. However, irrespective of the method used the following factors would affect the thickness of the slice and therefore also the size of the tumor.

(1) Inherent bias in grossing. It is extremely difficult to get a uniform tissue slice grossly, especially one that is as thin as 0.3 cm when the tissue is composed of different tissue types. A lumpectomy specimen typically has three components- fatty tissue (often predominant), fibrous tissue that is native to the breast and tumor tissue, typically associated with a fibrous reaction. After removal from the body, exterior forces holding the tissue together are disrupted and cause a spatial deformation of the tissue, and this affects each tissue type "differentially" [2]. Similarly, pressure applied to hold the specimen in place while sectioning would also create differential deformation of the tissue. Therefore, an average slice thickness measured at a "fatty area" in the slice, would not accurately reflect the thickness in the area of the tumor and cannot be used to calculate

the thickness of the tumor, especially when small numbers such as a few millimeters could change the stage. Indeed, this inherent spatial deformation may not allow for a 1:1 correlation of tumor size between *in vitro* grossing done at room temperature and *in vivo* tumor seen in a prone position on MRI at body temperature.

(2) No method for correcting for partial slice involvement: Tumor may have involved only a portion of a slice but by calculation it was counted as an entire slice. So in the example given below (**Figure 1**), the tumor involves slices 2, 3, and 4. It involves only partially, slices 2 and 4. By actual size this tumor is 0.7 cm in greatest dimension. By calculation, this tumor would measure 0.5 x 3 (3 slices are involved microscopically) or 1.5 cm.

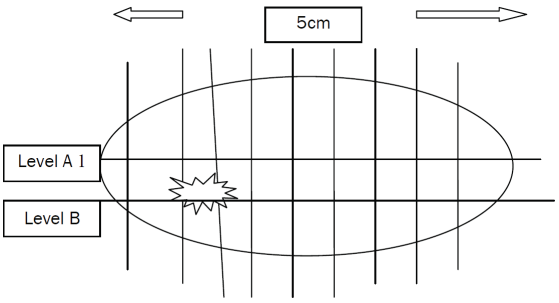

Figure 1. In the above diagram we highlight some of the problems with the method proposed by the authors. Note that tumor spans 3 slices, but only partially and minimally involves slices 2 and 4. Note also that slice 3 is narrower than the reset of the slices. In addition, slice 3 is slightly irregular such that a measurement at level A would result in a different measurement at Level B.

(3) Biopsy associated changes. Often, the difficulty calculating size has to do with a central biopsy cavity with tumor on either side. Is it reasonable to assume that the size of the cavity equals the size of the tumor? Hemorrhage and edema could expand (or fibrosis contract) the cavity and the "number of slices" may not reflect accurately the actual size of tumor.

We acknowledge that some of these are inherent and long-standing problems in the pathologic determination of invasive tumor size in breast cancers. It is imperative, however, that these problems be clearly understood by those involved in the management of breast cancer, and we are hesitant to endorse microscopic "amalgamations" or "estimations" as an undisputed gold standard when the determination of tumor size by this method is potentially fraught with so many possible sources of error.

Tumor size has emerged as a well-accepted prognostic factor, as well as a central basis for clinicopathologic staging, based on an extensive body of investigative work by numerous authors that encompassed epidemiologic, pathologic and clinical data [3]. The pathologic data in these studies regarding the methods of determining tumor size were not consistent, but the prognostic significance of tumor size has emerged nonetheless. In our opinion, there is simply insufficient evidence at present, and none is presented in this study, to assert that the microscopic determination of tumor size is a scientifically validated element that is unequivocally more accurate than gross measurement. To a large extent, this is a function of the absence of a true gold standard to which all the methods can be compared. The method proposed by the authors is as problematic as any other method that we have to date. This is because every microscopic examination is preceded by a "gross" evaluation, and is therefore subject to the inadequacies of a gross evaluation. Deficiencies inherent to measuring practices of grossing are multiplied many fold in the authors' method (here applied to the estimation of the size of the slice rather than that of the tumor). We would therefore suggest that a good gross examination, modified by a thorough microscopic examination and a detailed correlation between these modalities, is the best way to pathologically estimate the size of a given case of breast carcinoma. Methodologies that estimate tumor size based on the number of sections involved, constant multipliers, and section thicknesses, as applicable in DCIS for example [4], may have application in specific settings, such as in cases of lobular carcinoma where the gross methodology tends to be highly flawed and inaccurate. However, we are not convinced that these methods are better than the currently used methods in cases where the tumor is well visualized grossly.

Having said this, we do agree with the authors, that gross measurements can underestimate or overestimate the size of the tumor, and this is especially true of lobular carcinomas that may not necessarily incite the fibrous reaction that is "measurable" grossly. Indeed in our example, it

is reasonable to assume that tumor in slices 2 and 4 would not have been palpable, and the tumor would have been grossly estimated at 0.5 cm. Other well-established problems with gross estimation of tumor size include biopsy site changes, associated non-neoplastic proliferations, or a significant in-situ component, causing an overestimation of the invasive tumor size. However, the time-honored practice of correlating gross and microscopic impressions should resolve these problems in most cases.

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