International Journal of Surgery (2005) 3, 286–291

INTERNATIONAL JOURNAL OF SURGERY

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LETTERS TO THE EDITOR

Breast cancer surgery and angiogenesis: Stem cell cycle may explain heterogeneity of recurrence

Dear Editor

In the article by Retsky et al.[1] the first peak of recurrence is explained by the breaking of dormancy which occurs at surgery. Within this peak these authors propose two surgery-accelerated relapse modes, the first at 10 months due to avascular micrometastases stimulated to develop a vasculature and a second at 18–40 months resulting from single cells induced to proliferate. These two modes may exist and, although not addressed specifically in this publication, they may begin to explain differences in response to therapy which occurs for the first peak. However, they are insufficient to completely explain the differences in response. Demicheli et al.[2] compared women treated with mastectomy alone to women treated with mastectomy plus adjuvant CMF. The graphs of the hazard rate for treatment failure versus time revealed no effect on the timing of the first peak but decrease its height, the area under the curve and, therefore, the number of patients who recur at this time point. Likewise, Howell et al.[3] presented data from the ATAC trial at the 2004 San Antonio Breast Cancer Symposium which reveled that anastrozole produces the same result: patients treated with anastrozole had a decease in the height of the first peak. In both cases, however, there remain patients receiving therapy who recurred in the first peak. Why the lack of a uniform response? Inherent resistance is one possibility. I would argue that another possibility is that these dormant cells are breast cancer stem/progenitor cells which are residing in a stem cell niche in G_0. Beginning as early stem-cells, stem-cells mature through a number of stages eventually becoming committed progenitor cells and then mature, differentiated cells. Each of these types of stem-cells or progenitor cells theoretically can be the target of the transforming event(s). Tumors derived from early stem-cells, which by definition are mulitpotential, are hypothesized to lead to a more heterogeneous phenotype than those derived from later, differentiated cells. Tu et al.[4] have hypothesized that tumors derived from early stem-cells have increased metastatic potential. Because early stem-cells maintain their multipotentiality, it is also hypothesized that they have a more diversified growth factor and chemokine receptor profile which may be responsible for the increased metastatic potential. The cells responding to the act of operating may be early stem-cells propelled out of G_0 by a soluble, circulating substances released to promote wound healing. These early stem-cells would be predicted to produce heterogeneous recurrences only some of which are sensitive to chemo/endocrine/biologic therapy. This possibility will be important as perioperative therapies, e.g., antiangiogenic therapies suggested by the authors, are contemplated.

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doi: 10.1016/j.ijsu.2005.10.016

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Breast cancer heterogeneity may explain peaks in recurrence

Dear Editor

Dr. Retsky's[1] explanation for the early peak in recurrence rate in the early period after surgery is quite plausible and most interesting. Another possible explanation is the heterogeneity of the disease. There is variability in the rate of growth of breast cancers, with the more aggressive tumors recurring early. These are then removed from the at-risk population, leaving tumors that grow more slowly. Assuming at least a moderate proportion of aggressive tumors the effect would be a clear early peak in the recurrence rate. The longer term recurrence rate would be much lower than that in the early period following surgery. The rub, of course, is that today's science does not enable very accurate predictions of which tumors will recur early.

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doi: 10.1016/j.ijsu.2005.10.011

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Bradford-Hill Criteria provide the way ahead for controversial theory

Dear Editor

Retsky et al.'s paper[1] raises important questions about the possible role of surgery in promoting angiogenesis in early breast cancers. This is another piece of evidence relevant to the question of whether screening for cancers in women under 50 is beneficial (reduces mortality) or possibly