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To Measure the Unmeasurable

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In their article Takahido Shien and colleagues from the National Cancer Center Hospital in Tokyo, report their experiences with using clinical and pathological tumor features as predictors of the response of breast tumors to neoadjuvant chemotherapy [1].

Neoadjuvant chemotherapy is widely used to downsize primary tumors and facilitate subsequent resection or breast conservation, both in locally advanced disease and in the earlier stages of operable breast cancer. The overall response rate is usually good (between 70% and 90%), but the extent of the tumor response and shrinkage varies greatly between individual patients.

Being able to predict the eventual outcome of neoadjuvant chemotherapy would be of great value in providing information to patients and their physicians about what can be achieved by taking this preoperative approach. Outcome data could allow for informed decision making and balancing potential benefits against side effects and risks. A recent report has been indicated that endocrine responsive and lobular cancers are less likely to respond very well to neoadjuvant chemotherapy [2].

In general, it is agreed that only complete pathological remission (pCR) will lead to an overall survival benefit for the patient [3], and this has blighted the initial enthusiasm over the advantages of neoadjuvant chemotherapy. It is known that partial remissions—i.e., reductions in tumor volume of more than 50%—fail to yield significant long-term benefit [4]; yet, surprisingly, the biology that underlies this observation remains unclear.

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Shien et al. reported that they found that what they call "scirrhous-type" tumors would less likely show a pCR. For reduction of tumor size (defined as reduction of size by 30% in their article), high-grade tumors and tumors appearing "localized" on computerized tomography (CT) scans were more likely to respond. Scirrhous-type tumors may reflect lobular cancers, which do not respond well to neoadjuvant chemotherapy. High-grade tumors are generally believed to be more sensitive to chemotherapy than low-grade tumors; however, it remains difficult to explain, in terms of tumor biology, what "localization" of the tumor means.

The study by Shien et al. reports interesting findings; however, it also has several weaknesses: CT is not widely used on a global basis for tumor evaluation during neoadjuvant treatment because of the radiation involved, and because the accuracy of the scans is often inferior to mammography and magnetic resonance imaging (MRI), both of which are widely accepted imaging techniques [5]. Also, it is well known that response to neoadjuvant chemotherapy will depend on other factors, such as p53 overexpression and the chemotherapy protocol used: for example, clinical experience shows that anthracyclins lead to concentric shrinkage of tumors, whereas taxanes often result in a more scattered pattern of residual tumor [6].

Furthermore, Shien et al. suggest a system of response evaluation based on clinical measurements of tumor sizes. This is obviously scientifically dangerous: not only because the surgeon will often overestimate the actual responses of neoadjuvant treatment during palpation and caliper measurements, but also because a generally accepted, objective measurement system must be established. Surgeons may or may not like the WHO/RECIST response criteria of CR/PR/NC/PD [7], but it has obvious advantages to avoid reinventing the wheel again and again.

Furthermore the overall breast conservation rate that Shien et al. report for their cohort is very low compared with international standards, and this has the potential for giving away some of the benefits of the preoperative treatment. Although the reported overall response rate of 85% and the pCR rate of 15% are typical for the chemotherapy regimens used, the reported breast conservation rate of 37% is rather disappointing. In reality, that means that not even 50% of patients could eventually clinically benefit from their documented response to neoadjuvant chemotherapy. In most experienced centers, for a cohort of patients as described, with a median tumor size of 24 mm, a breast conservation rate of 60%−80% appears achievable. This should be a call to surgeons: when we subject our patients to the side effects of chemotherapy, we should maintain an aggressive breast-conservation policy—something that can be done safely [8].

In summary, it is necessary to stay focused when trying to resolve the important question of predicting response accurately and—perhaps even more important—monitoring tumor changes during neoadjuvant chemotherapy. Most likely, the solution will not be found in the morphological or numerical properties of the primary tumors. Particularly as surgeons, we need to say farewell to overly mechanistic, numerical or phenotypical approaches. The answer for these challenges lies in the detailed biology of the tumors and their hosts, and molecular techniques will eventually help us to shed light on what is happening during such treatment interventions.

Accurate prediction that will guide both patients and physicians in their strategy decisions will only be an obvious first step. The real goal remains to gain the ability both to investigate the eventual individual tumor response and to monitor ongoing responses and eventually adapt the treatment regimens and or strategies to the individual situation. Several technologies to achieve that goal have been proposed [9]. The reality test, however, will come from a precise, two-pronged clinical trial, randomizing a classical approach with a fixed regimen versus a "biologically monitored" experimental arm with optimized treatments. Such research is difficult to undertake for several reasons, some of which are outline above, yet it is urgently needed.

References

1. Shien T, Akashi-Tanaka S, Miyakawa K (2008) Clinicopathological and imaging classification of tumors as predictors of the efficacy of neoadjuvant chemotherapy for operable breast cancer. World J Surg. doi:10.1007/s00268-008-9800-9 [Epub ahead of print]
2. Wenzel C, Bartsch R, Hussian D et al (2007) Invasive ductal carcinoma and invasive lobular carcinoma of breast differ in response following neoadjuvant therapy with epidoxorubicin and docetaxel + G-CSF. Breast Cancer Res Treat 104:109–114
3. Buzdar AU (2007) Preoperative chemotherapy treatment of breast cancer—a review. Cancer 110:2394–2407
4. Mieog JS, van der Hage JA, van de Velde CJ (2007) Neoadjuvant chemotherapy for operable breast cancer. Br J Surg 94:1189–1192
5. Schegerin M, Tosteson AN, Kaufman PA et al. (2008) Prognostic imaging in neoadjuvant chemotherapy of locally-advanced breast cancer should be cost-effective. Breast Cancer Res Treat. 25 April [Epub ahead of print]
6. Esteva FJ, Hortobagyi GN (2008) Can early response assessment guide neoadjuvant chemotherapy in early-stage breast cancer? J Natl Cancer Inst 100:521–523
7. Marcus CD, Ladam-Marcus V, Cucu C, et al. (2008) Imaging techniques to evaluate the response to treatment in oncology: current standards and perspectives. Crit Rev Oncol Hematol. 28 August [Epub ahead of print]
8. Soucy G, Bélanger J, Leblanc G et al (2008) Surgical margins in breast-conservation operations for invasive carcinoma: does neoadjuvant chemotherapy have an impact? J Am Coll Surg 206: 1116–1121
9. Goldstein NS, Decker D, Severson D et al (2007) Molecular classification system identifies invasive breast carcinoma patients who are most likely and those who are least likely to achieve a complete pathologic response after neoadjuvant chemotherapy. Cancer 110:1687–1696