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In their guidelines for managing locally advanced breast cancer, Tamara Shenkier and associates1 mention the difficulty they faced in dealing with changes that were made to the tumour–node–metastasis (TNM) tumour-staging system in 2002 (Table 1). Their comment on this point needs amplification because, if anything, it understates the potential confusion caused by the introduction of a new category, stage IIIIC.

Stage IIIIC is defined as applying to patients with any T category and pN3 disease (Table 2). pN3 disease in turn has 3 subcategories, the third of which (pN3c), supraclavicular node involvement, is the focus of the comments by Shenkier and associates.1 As they state, there is now some evidence to support treating these patients as having inoperable locally advanced, rather than metastatic, disease. However, pN3a and pN3b represent types of nodal involvement (more than 10 axillary, infraclavicular and internal mammary nodes) that have little or nothing to do with operability. Most such patients would be managed in the manner that Shenkier and associates describe for operable stage IIIA disease.

It is unfortunate that the newly introduced stage IIIC category includes 2 groups of patients for whom management strategies are quite different. Indeed, its utility as a descriptive category must be questioned, particularly in the context of management guidelines. In this setting it might have been better to use specific T and N categories, since the guideline as published appears to imply that stage IIIC is equivalent to supraclavicular node involvement.

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Table 1: TNM staging system for breast cancer

| Stage | Tumour status* | Node status† | Metastasis status‡ |
|-------|---------------|--------------|-------------------|
| 0     | Tis           | N0           | M0                |
| I     | T1            | N0           | M0                |
| IIA   | T2            | N0           | M0                |
| IIIB  | T2            | N0           | M0                |
| IIIA  | T2            | N0           | M0                |
| IV    | Any T         | Any N        | M0                |

* Tumour status: Tis = carcinoma in situ; T1 = no evidence of primary tumour; T2 = tumour ≤ 2 cm in greatest dimension; T3 = tumour > 2 cm but not > 5 cm in greatest dimension; T4 = tumour > 5 cm in greatest dimension; T4 = tumour of any size with chest-wall extension, ulceration, peau d’orange or inflammatory breast cancer.
† Node status: N0 = no regional lymph-node metastasis; N1 = metastasis in movable ipsilateral axillary lymph nodes; N2 = lymph-node metastasis in clavicular or supraclavicular lymph nodes.
‡ Metastasis status: M0 = no distant metastasis; M1 = distant metastasis.

Table 2: Definitions of pN3 breast cancer and its subcategories

| Category | Definition† |
|----------|-------------|
| pN3      | Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph node(s) in the presence of 1 or more positive axillary lymph node(s); or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes. |
| pN3a     | Metastasis in 10 or more axillary lymph nodes (at least one tumour deposit > 2.0 mm), or metastasis to the infraclavicular lymph nodes. |
| pN3b     | Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent. |
| pN3c     | Metastasis in ipsilateral supraclavicular lymph nodes. |
The incorporation of taxanes into adjuvant therapy of breast cancer has been a matter of great interest. Several randomized trials have demonstrated a survival advantage for patients treated with taxanes, such as doxorubicin and paclitaxel. However, the risk of myeloid and lymphoid leukemia has been a concern, particularly in patients treated with anthracycline-based regimens.

In a recent study, the NCIC CTG recently analyzed the risk of leukemia in 4 trials of adjuvant chemotherapy. The conditional probability of myeloid and lymphoid leukemia was 1.7% for epirubicin-containing regimens and 1.3% for AC. In a series of trials conducted by the NSABP, the rate of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) with standard-dose AC was 0.21%. Paclitaxel does not appear to increase this risk. In a recent study there were 8 cases (0.5%) of MDS or AML among 1580 patients treated with AC and the same number in 1590 patients treated with AC and paclitaxel. The leukemia risk for docetaxel-based regimens has not yet been reported. Although treatment-related leukemia risk is an important issue for patients with early breast cancer and a good overall prognosis, patients with a high competing risk of death from breast cancer do not have the same risk of this complication. This point was exemplified by a randomized trial comparing CEF with intensified epirubicin and cyclophosphamide in patients with locally advanced breast cancer. In that trial, there were no reported cases of MDS or AML in the 224 patients who received CEF.

Joe Pater addresses the difficulty of writing guidelines when the sand is shifting with respect to inclusion criteria. We agree that those with isolated supraclavicular involvement (N3c disease) should be treated as having inoperable locally advanced disease. There is some rationale for including patients with clinically apparent internal mammary node (N3b) disease in that category as well. Patients who are found to have extensive lymph node involvement (more than 10) postoperatively should be treated with adjuvant and not primary chemotherapy.

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