or locally advanced breast cancer. *CMAJ* 2004; 170(6):983-94.
2. Henderson IC, Berry DA, Demetri GD, Cirrincione CT, Goldstein LJ, Martino S, et al. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol* 2003;21(6):976-83.
3. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003;21(8):1431-9.
4. Levine MN, Bramwell VH, Pritchard KI, Norris BD, Shepherd LE, Abu-Zahra H, et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1998;16:2651-8.
5. Piccart MJ, Di Leo A, Beauduin M, Vindevoghel A, Michel J, Focan C, et al. Phase III trial comparing two dose levels of epirubicin combined with cyclophosphamide with cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer. *J Clin Oncol* 2001;19(12):3103-10.

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In their guidelines for managing locally advanced breast cancer, Tamara Shenkier and associates[1] 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 IIIC.

Stage IIIC 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[2]

Stage	Tumour status*	Node status†	Metastasis status‡
0	Tis	N_0	M_0
I	T_1	N_0	M_0
IIA	T_0	N_1	M_0
	T_1	N_1	M_0
	T_2	N_0	M_0
IIB	T_2	N_1	M_0
	T_3	N_0	M_0
IIIA	T_0	N_2	M_0
	T_1	N_2	M_0
	T_2	N_2	M_0
	T_3	N_1	M_0
	T_3	N_2	M_0
IIIB	T_4	N_0	M_0
	T_4	N_1	M_0
	T_4	N_2	M_0
IIIC	Any T	N_3	M_0
IV	Any T	Any N	M_1

*Tumour status: Tis = carcinoma in situ; T_0 = no evidence of primary tumour; T_1 = tumour ≤ 2 cm in greatest dimension; T_2 = tumour > 2 cm but not > 5 cm in greatest dimension; T_3 = tumour > 5 cm in greatest dimension; T_4 = tumour of any size with chest-wall extension, ulceration, peau d'orange or inflammatory breast cancer.
†Node status: N_0 = no regional lymph-node metastasis; N_1 = metastasis in movable ipsilateral axillary lymph node(s); N_2 = metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph-node metastasis; N_3 = metastasis in ipsilateral internal mammary lymph node(s) or in ipsilateral supraclavicular lymph node(s).
‡Metastasis status: M_0 = no distant metastasis; M_1 = distant metastasis.

Table 2: Definitions of pN3 breast cancer and its subcategories

Category	Definition[3]
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 node(s); 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

References
1. Shenkier T, Weir L, Levine M, Olivetto I, Whelan T, Reyno L; Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer. *CMAJ* 2004;170(6):983-94.
2. Singletary SE, Allred C, Ashley P, Bassett LW, Berry D, Bland KI, et al. Revision of the American Joint Committee on Cancer Staging System for Breast Cancer. *J Clin Oncol* 2002;20(17): 3628-36.
3. *Breast cancer (PDQ®): treatment, health professional version* [online]. Bethesda (MD): National Cancer Institute; 2004. Available: www.cancer.gov/cancerinfo/pdq/treatment/breast/healthprofessional/#Section_27 (accessed 2004 May 7).

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[Three of the authors respond:]

As Sunil Verma and associates note, evidence is rapidly accumulating that aromatase inhibitors offer advantages over tamoxifen in terms of efficacy and toxicity.[1-3] However, none of these studies has shown an overall survival advantage. At the time our guidelines[4] were submitted, there had not yet been a change in treatment policy incorporating these agents. Although the cited studies did not specifically include patients with locally advanced breast cancer, it is reasonable to extrapolate findings from trials in the setting of early breast cancer to the setting of locally advanced breast cancer.

Two randomized studies have used neoadjuvant aromatase inhibitors in postmenopausal patients with operable tumours. After 4 months, the complete response rate, on the basis of pathological evidence, was only 1%.[5,6] However, for patients with inoperable disease who are not eligible for chemotherapy, we would not recommend an aromatase inhibitor alone outside of a clinical trial. Combined-modality therapy with locoregional irradiation and a systemic hormonal manoeuvre would still be the standard of care.

The incorporation of taxanes into adjuvant therapy is also evolving rapidly.[7] The update on the Aberdeen trial[8] was presented after our manuscript was submitted. Although only 97 patients were randomized, the Aberdeen study is important because it included only patients with locally advanced breast cancer and because it showed a significant survival benefit for patients who responded to cyclophosphamide, vincristine, doxorubicin and prednisone (CVAP) (4 cycles) and were subsequently switched to docetaxel (4 cycles) instead of receiving 4 more cycles of CVAP. If this survival advantage is confirmed by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 study,[7] there will be further compelling evidence for a taxane-based approach. Another recently presented study demonstrated a survival advantage of adjuvant docetaxel, adriamycin and 5-fluoruracil over 5-fluorouracil, adriamycin and cyclophosphamide.[9] However, to date, no taxane-based regimen has shown superiority over an adequately dosed anthracycline-based regimen using oral cyclophosphamide, such as CEF (oral cyclophosphamide with intravenous epirubicin and 5-fluorouracil).[10] This is one question being addressed by the randomized trial MA.21 of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG).

We agree with Deepu Mirchandani and colleagues that the risk of leukemia should be discussed with any patient undergoing anthracycline-based chemotherapy. The NCIC CTG recently analyzed the risk of leukemia in 4 trials of adjuvant chemotherapy.[11] 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%.[12] 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.[13] The leukemia risk for docetaxel-based regimens has not yet been reported.[7] 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.[14] 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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References
1. Baum M, Buzdar AU, Cuzick J, Forbes J, Houghton JH, Klijn JG, et al; ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;359:2131-9.
2. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003;349:1793-802.
3. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004;350(11):1081-92.
4. Shenkier T, Weir L, Levine M, Olivotto I, Whelan T, Reyno L; Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice