

CONFERENCE PREVIEW: JOINT CANCER CONFERENCE 2000 II. CLINICAL RESEARCH

1. RECENT ADVANCES IN THE TREATMENT AND OUTCOME OF LOCALLY ADVANCED RECTAL CANCER

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In 1998, there were 36,000 new cases of rectal cancer in the United States. Colorectal cancer is the third leading cause of cancer deaths in both men and women, ranking behind lung and prostate for men and lung and breast for women. In 1998, an estimated 8,800 deaths were caused by rectal cancer and 56,500 by all colonic cancers. In 1963, the five-year relative survival rate for all patients with rectal cancer was only 38%. This figure had risen to 61% by 1993. The improvement is due to earlier detection and advances in treatment.

Locally advanced rectal cancer is defined as a large, often circumferential lesion that penetrates through the entire thickness of the rectal wall into the surrounding mesenteric fat. Lymph nodes usually contain metastatic cancer. The cancer might be fixed to the side walls of the pelvis, to the prostate in men, or to the vagina in women. These lesions are frequently difficult to resect and often require removal of the anal sphincter with a permanent colostomy. Treatment with surgery alone results in survival rates much below 50%, and local recurrence rates are variously reported to be between 30% and 50%. These local recurrences in the pelvis often are not amenable to

treatment and result in chronic pain, ulceration, and bleeding prior to death.

In 1992, our group at the University of Florida College of Medicine reported the results of 148 patients with locally advanced rectal cancer who had received preoperative radiation therapy in an attempt to shrink the tumor size, reduce local recurrence, and increase the opportunity for anal sphincter preservation.¹ Most institutions at that time were using radiation therapy only postoperatively. The aim of this approach was to reduce local recurrence by having the radiation kill any residual tumor cells left behind in the pelvis at the time of the operative procedure. Radiation therapy was not thought to provide any survival advantage. However, we found that there was an absolute survival advantage at five years for patients who were treated with preoperative radiation therapy compared to historical control patients who were treated with surgery alone (66% vs 40%, respectively, $P=0.0001$) (Figure). This observation has now been confirmed in several randomized, prospective control trials.^{2,5}

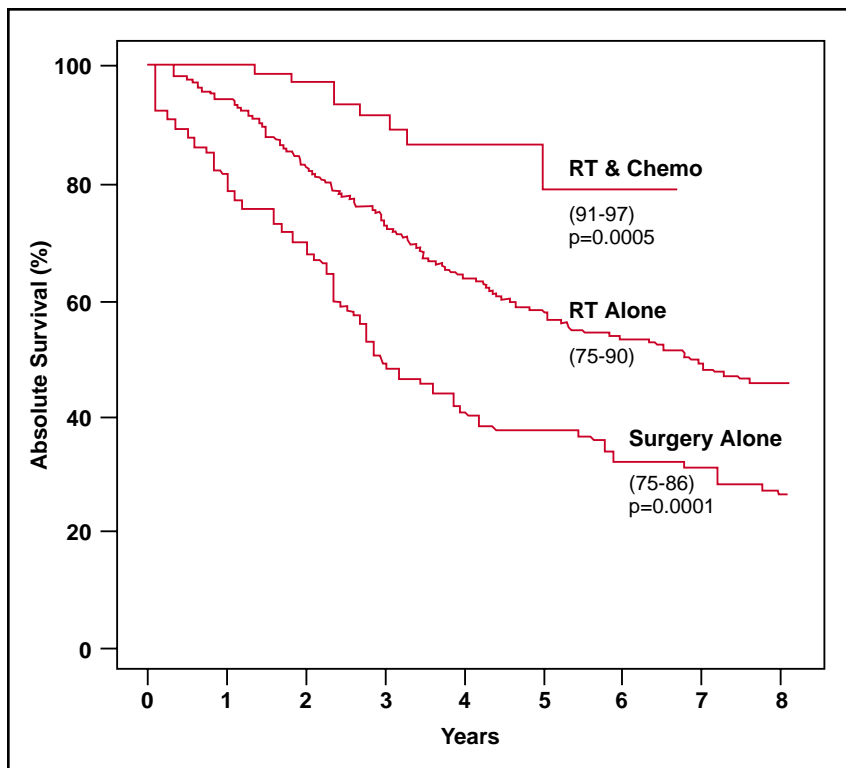
Chemotherapy, specifically 5-fluorouracil (5-FU), is known to

sensitize cancer cells to the lethal effects of radiation therapy. In 1991, we combined 5-FU with radiation therapy preoperatively in the treatment of locally advanced rectal cancer. This report compares the outcome of patients in our institution who were treated in an early era of radiation therapy alone (1975 to 1990) to those treated in the late era with the combined modality of both radiation and chemotherapy preoperatively (1991 to 1997).⁶ There were 219 patients in the early era and 109 patients in the late era. The number of circumferential and fixed lesions in both eras was equal. There was no significant difference in patient age or in the distance of the lesions from the anus. Lesions shrunk in size dramatically

with combined therapy as proven by digital rectal examination, computed tomography, transrectal ultrasound, and/or rectal magnetic resonance imaging. In fact, a complete tumor response with no residual cancer identifiable pathologically in the resected specimen occurred in 28% of the patients in the late era (those treated with continuous chronobiologic infusion of 5-FU) compared to 8% of patients treated in the early era (with radiation therapy alone). Because of the decrease in the size of the rectal cancer and improvement in surgical techniques, sphincter-preserving procedures could be done in 52% of the patients who received radiation and chemotherapy as opposed to

only 13% of patients who received radiation therapy alone. Thus, the ability to eliminate the need for a permanent colostomy quadrupled between these two eras.

The stage of the disease preoperatively prior to radiation therapy and chemotherapy can be compared to the stage of disease in the resected pathologic specimen postoperatively. Any discordance between these two could be secondary to inaccurate clinical staging or to the salutatory effects of preoperative treatment. Computed tomography, magnetic resonance imaging, and transrectal ultrasound allow us to clinically stage patients accurately. All patients in both eras had clinical stage T3 or T4 rectal cancers, meaning full-thickness penetration through the bowel wall into the mesenteric fat with possible invasion of adjacent organs. Both radiation therapy alone and combined treatment downstaged patients to either T0 (no residual tumor), T1 (tumor limited to the internal lining of the rectum), or T2 (tumor limited to the muscular wall of the rectum). This downstaging occurred in 42% of patients using radiation therapy alone and in 58% of patients with combined modality treatment ($P < 0.001$). Rather than having their survival predicted by their clinical stage (30% to 50%), the survival appears to be determined by the pathologic stage. The one-, three-, and five-year overall survivals comparing the late era with the early era are 100%, 92%, and 87% vs 95%, 73%, and 58%, respectively ($P = 0.0005$). Thus the addition of chemotherapy to the radia-



Survival following treatment for rectal cancer.

Effect of Chemotherapy Added to Preoperative Radiation on Complete Response Rate*

Study Site (ref)	Chemotherapy	Complete Response
University of Florida (1)	None	8%
Jewish Hospital (7)	None	6%
M.D.Anderson Cancer Center (8)	5-FU	29%
Duke University Medical Center (9)	5-FU, cisplatin	27%
Memorial Sloan-Kettering Cancer Center (10)	5-FU, leucovorin	20%
University of Florida (2)	5-FU, leucovorin	28%

*All patients received 40 to 50 Gy of radiation therapy.

tion therapy protocol resulted in a distinct survival advantage (Figure).

The addition of chemotherapy to the radiation therapy preoperative protocol has improved overall survival significantly in this non-randomized study. The frequency of local recurrence (14%) and lymph node involvement (21%) was unchanged between eras, meaning that systemic chemotherapy probably eliminated distant micrometastasis. Our observations must be substantiated by randomized, prospective control trials as was done with our observations with preoperative radiation therapy alone. The addition of 5-FU (with or without leucovorin) to radiation therapy preoperatively has already been shown to convert many patients to candidates for sphincter preservation operations rather than abdominoperineal resection with a permanent colostomy. Likewise, multiple institutions are reporting a greater complete response rate (T0) with chemoradiation compared to radiation therapy alone (Table).⁷⁻¹⁰

Another potential benefit from downstaging, especially to T0, may

be the ability to locally excise the residual scar in the rectum that remains after treatment. This procedure can be done transanally, thereby eliminating the need for any abdominal operation. Transanal excision of downstaged rectal cancers should be considered an experimental procedure, the candidates for which have not yet been fully determined. Nevertheless, preoperative chemotherapy for malignancies of organs other than the rectum has allowed a more limited resection with equal results when compared to those results of prior radical resections. A good example is the ability to preserve the breast with a limited resection after reducing a bulky breast cancer with preoperative chemotherapy.

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of the faculty of the University of Florida College of Medicine.

References

1. Mendenhall WM, Bland KI, Copeland EM 3d, et al. Does preoperative radiation therapy enhance the probability of local control and survival in high-risk distal rectal cancer? *Ann Surg.* 1992;215:696-706.
2. Neto JAR, Quilici FA, Reis JA. A comparison of nonoperative vs preoperative radiotherapy in rectal carcinoma. *Dis Colon Rectum.* 1989;32:702-708.
3. Marsh PJ, James RD, Schofield PF. Adjuvant preoperative radiotherapy for locally advanced rectal carcinoma: results of a prospective, randomized trial. *Dis Colon Rectum.* 1994; 37:1205-1214.
4. Randomized study on preoperative radiotherapy in resectable rectal cancer. Stockholm Colorectal Cancer Study Group. *Ann Surg Oncol.* 1996;3:423-430.
5. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med.* 1997;336:980-987.
6. Vauthey JN, Marsh RW, Zlotecki RA, et al. Recent advances in the treatment and outcome of locally advanced rectal cancer. *Ann Surg.* 1999;229: 745-754.
7. Myerson RJ, Michalski JM, King ML, et al. Adjuvant radiation therapy for rectal carcinoma: predictors of outcome. *Int J Radiat Oncol Biol Phys.* 1995;32:41-50.
8. Rich TA, Skibber JM, Ajani JA, et al. Preoperative infusional chemoradiation for stage T3 rectal cancer. *Int J Radiat Oncol Biol Phys.* 1995;32: 1025-1029.
9. Chari RS, Tyler DS, Anscher MS, et al. Preoperative radiation and chemotherapy in the treatment of adenocarcinoma of the rectum. *Ann Surg.* 1995;221:778-787.
10. Minsky BD, Cohen AM, Kemeny N, et al. Enhancement of radiation-induced downstaging of rectal cancer by fluorouracil and high-dose leucovorin chemotherapy. *J Clin Oncol.* 1992;10:79-84.

2. SIGNIFICANCE OF SENTINEL NODE MICROMETASTASIS

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The emergence of sentinel lymph node (SLN) biopsy as an alternative method to axillary dissection for staging the axilla in breast cancer patients has brought the value of axillary dissection into close scrutiny. In addition, it has stimulated the assessment of the biologic implications of micrometastatic disease to lymph nodes. Historical review of SLN technology demonstrates that micrometastatic disease in SLNs may be critical in the evaluation of false-negative SLNs. Furthermore, the presence of micrometastatic disease in the lymph nodes may carry prognostic significance for the overall behavior of the malignancy.

Historical Perspective

False-Negative Evaluation

In the initial trial of SLN mapping for melanoma, 10 (4.1%) of 243 patients developed recurrent disease in the basin from which the initial SLN was removed. These lymph nodes were evaluated after blue dye localization with routine hematoxylin-eosin (H&E) stains on bivalved SLNs. Within 18 months of the evaluation, these patients recurred. However, upon multiple recuts of the SLNs with evaluation by S-100 stains, 7 of 10 patients' sentinel nodes were detected to

have micrometastases.¹ This observation raised the significant question as to whether the false-negative evaluations could have been precluded if the micrometastases had been detected upon initial evaluation. Several of the initial trials evaluating SLNs in breast cancer have similarly avoided the detection of micrometastases by cytokeratin analysis or multiple sections of the SLN. The avoidance of these tests was based on the presumption that the detection of small micrometastatic disease would not alter the management of a patient with breast cancer. Therefore, these studies have demonstrated false-negative rates between 5% and 11%.^{2,3} A significant observation demonstrated that 3 (11%) of 27 patients, in whom cytokeratin immunohistochemistry (IHC) detected micrometastatic cells in SLNs, also had additional metastases detected in the remaining lymph nodes on complete axillary dissection. Therefore, we conclude that careful evaluation of SLNs for micrometastatic disease obviates the false-negative assessment of the axilla in breast carcinoma, a historical lesson learned with melanoma.

Prognostic Significance of Micrometastases in Melanoma

A seminal observation made by Heller et al⁴ demonstrated that

30% of histologically negative lymph nodes harbored metastatic melanoma cells detected by growth in tissue culture. The subsequent evaluation by the same group, using reverse-transcription polymerase chain reaction (RT-PCR) for tyrosinase in melanoma, demonstrated expression of the enzyme in 30% of histologically negative lymph nodes.⁵ Shivers et al⁶ have demonstrated that melanoma patients with RT-PCR-negative SLNs have a recurrence rate of less than 1% at five years following initial surgery. This finding makes RT-PCR results the single most important prognostic indicator of survival in melanoma.

The historical lessons learned with SLN mapping in melanoma should not be repeated with breast cancer (ie, detection of false-negative SLNs in breast cancer, as with melanoma, can be minimized by IHC staining of SLNs). Furthermore, the prognostic significance of micrometastatic SLN involvement may prove, as with melanoma, to have profound consequences in determining which patients are at risk for distant metastatic disease. Several studies to date have demonstrated that micrometastatic disease in breast cancer may indeed have therapeutic significance for breast cancer patients. This paper examines the evidence to date and reviews these findings.

Direct Evidence Supporting the Significance of Micrometastatic Disease

An accumulating body of evidence supports the hypothesis that the presence of otherwise occult or clandestine micrometastatic nodal disease has a significant effect on recurrence rates and overall survival (OS) for breast cancer patients (Table).⁷⁻¹⁵ Whereas the world's literature contains numerous conflicting observations with regard to the significance of micrometastatic disease, most of the carefully performed, larger analyses (>300 patients) demonstrate a negative impact for this histologic finding.

The most thorough study to date was performed by the International (Ludwig) Breast Cancer Study Group.⁷ This trial re-reviewed find-

ings of 921 breast cancer patients without evidence of distant metastatic disease and classified them as having node-negative disease on routine pathologic evaluation. Almost all were resected at six levels with six 3-mm sections cut at each level, two of which were stained with H&E.⁸ Only parenchymal node metastases were recorded as micrometastases. Serial sectioning identified occult micrometastatic deposits in 83 (9%) of 921 patients, with more than one affected node detected in 13 (15.6%) of 83 cases. The effect of finding previously occult micrometastatic disease on survival in this study was clear: at both five and six years of follow-up, both disease-free survival (DFS) rates and OS rates were significantly affected. At a median follow-up of six years, DFS was reduced from 71% in the node-negative group to 53% in the node-positive group ($P=0.0008$) and OS was reduced from 86% in the node-negative group to 70% in the

node-positive group ($P=0.0009$). Interesting biologic correlates observed in this trial included an association between occult micrometastatic disease and larger tumors ($P=0.02$), histologic grade ($P=0.05$), vascular invasion ($P<0.0001$), and age <50 years ($P<0.0001$).^{7,8}

A second retrospective trial re-examining nodal tissue previously classified as negative was performed by Hainsworth et al.¹² This study examined the value of IHC staining in 343 patients previously assessed as having node-negative breast cancer. Using antimucin monoclonal antibodies, occult metastases were detected in 41 patients (12%). Most occult micrometastases were <2 mm in size and were confirmed by H&E using serial sections. At a median follow-up of 79 months, the presence of occult micrometastases in two or more nodes reduced the DFS from 84% to 54% ($P<0.01$) and OS from 85% to

Previous Reports of Micrometastatic Lymph Node Disease: The Largest Trials

Author	Number of Patients	Technique	% Micrometastatic (M) or Occult (%)	Disease-free Survival	Overall Survival
Ludwig Breast Cancer Study ^{7,8}	921	SS	9 (O)	0.003	0.002
de Mascarel et al ⁹	1,680	SMS	7 (M)	0.008	0.036
	129	IHC	10 (M)	0.01	NS
Wilkinson et al ¹⁰	525	SS	17 (O)	NS	NS
Friedman et al ¹¹	1,153	SMS	23 (M)	RR = 1.7	
Hainsworth et al ¹²	343	IHC	12 (O)	0.01	0.05
Fisher et al ¹³	566	Survey	8 (M)	NS	
Clayton and Hopkins ¹⁴	399	Survey	15 (M)	NS	
Trojani et al ¹⁵	150	IHC	14 (M)	0.0025	0.02

SS = serial section
 SMS = serial macroscopic section
 IHC = immunohistochemistry
 NS = not statistically significant
 RR = relative risk

70% ($P<0.01$). This study and one by Trojani et al¹⁵ of 162 patients with node-negative breast cancer both demonstrated the beneficial impact of IHC staining in detecting micrometastases as well as the negative impact of micrometastases on DFS and OS rates.

Although studies re-examining nodal tissues that were previously declared negative for the presence of occult disease are informative, another approach to this problem has been to perform prospective analyses attempting to identify all occult nodal disease on the initial review. In a study by de Mascarel et al,⁹ 1,680 patients were subjected to a standard method of node sectioning (serial macroscopic section, SMS). This method of serial sectioning is designed to sample nodes more effectively by cutting each node into slices 1.5 mm in thickness, each of which is assessed. In this study, micrometastases were defined as lesions <0.5 mm. Of 1,680 patients, 336 were identified as node-positive, with 120 having a single micrometastasis (<0.5 mm). With median follow-up of seven years, both the DFS ($P=0.005$) and OS ($P=0.0369$) were significantly reduced in those patients with a single micrometastasis compared to those declared node-negative.

In a similar trial by Friedman et al,¹¹ 1,153 breast cancer patients underwent prospective SMS nodal analysis. This study examined the impact of the anatomic location of micrometastases (parenchymal vs peripheral sinus). Of these patients, 637 (55%) were found to be

node-negative, 41 (3.5%) were found to have a single focus in the parenchyma, and 205 (8%) were found to harbor one peripheral sinus micrometastasis. Again, this trial found an increase in relative risk associated with presence of parenchymal micrometastasis (RR = 1.7) or peripheral sinus micrometastasis (RR = 1.7, $P=0.05$)

Conflicting Evidence Suggesting No Impact of Micrometastatic Disease

Many of the initial reports concerning the effect of nodal micrometastasis on breast cancer were negative studies unable to reach statistical significance. Unfortunately, however, many of these studies were performed without resectioning nodes previously classified as node-negative, or they involved sample sizes that were too small. Instead, several of the studies simply identified the presence of random micrometastases in nodes assessed by standard pathologic techniques (such as one H&E-stained section analyzed per node). This sort of minimal analysis, avoiding meticulous and serial sectioning methods with or without the use of IHC staining, yields an accurate numerator (number of micrometastases) without a correct denominator (number of nodes without micrometastasis). One example of this form of analysis is found in a trial reported in 1978 by Fisher et al.¹³ In this prospective trial, one section from each node of 566 patients was examined by routine H&E staining for the presence

of metastatic nodal disease. If a nodal metastasis was identified and was <2 mm, it was classified as a micrometastasis. It is easy to see how this sort of classification scheme measures a completely different set of biologic data from methods designed to identify occult micrometastatic disease. In this study, 8% of patients were found to have micrometastases, according to the investigators' definition. This classification resulted in no effect on OS, although treatment failure rates in this group approached failure rates found in patients with micrometastases. The authors concluded that their sample sizes were likely too small to detect significant differences using their experimental approach. They further predicted that a sample size of 1,400 would need to identify a 10% difference in OS with a confidence interval of 95%.

Another similarly performed study by Clayton and Hopkins¹⁴ reported in 1993 re-examined 399 node-positive patients for the presence of micrometastases <2 mm in size. Of these patients, 62 were classified as harboring micrometastasis, yet when survival rates were compared with those of node-negative patients, no differences in OS were identified. Again, no attempt at serial sectioning was made in this retrospective study.

The majority of older studies of micrometastatic disease inadequately addressed the issue and therefore can be dismissed. However, a study by Wilkinson et al¹⁰ appears to have carefully assessed the significance of micrometastatic disease, although

the sample size was likely too small. In this study, 525 cases of node-negative breast cancer with five or more years of follow-up were selected for further analysis. Negative nodes were resected in serial fashion and inspected using routine H&E histologic methods. On average, 24 sections were examined from each lymph node, and 84 (17%) cases of occult metastases were found. In addition, five cases of "overlooked" micrometastases were detected on reevaluation of the original pathologic slides. Despite finding these occult lesions, no significant difference in OS could be demonstrated. There was, however, a reduced survivorship ($P=0.003$) associated with micrometastases that were overlooked on initial pathologic review. The results of this study are curious and contradict the findings of numerous other positive studies. It is difficult to explain why this fairly large study failed to show a disadvantage to occult micrometastases, whereas smaller trials have found significant differences. This discrepancy is particularly concerning because the presence of occult micrometastases was linked to lymphovascular invasion in the primary tumors ($P<0.0005$). Therefore, we concluded that a lack of survival significance may be related to the relatively small sample size and lack of incorporation of IHC techniques to improve the detection of micrometastases. In other words, analysis of large numbers of serial sections is inadequate to determine the ultimate significance of micrometastasis unless more patients are studied or more sensitive methods are used to detect these lesions.¹⁶

Micrometastatic Disease Linked to Sentinel Lymph Node Biopsy

Although micrometastatic disease is biologically important, it appears to be an uncommonly observed event unless special pathologic sectioning or staining techniques are used. These techniques have generally been considered too labor-intensive and cost-ineffective for routine implementation. Recently, however, with the introduction of SLN biopsy, it has become feasible to incorporate some of the more sensitive pathologic methods into routine clinical practice. For example, although it is standard practice to analyze one or two sections from each sampled axillary lymph node by H&E staining, it is now possible to perform serial sectioning of a few SLNs for the same cost. In addition, the use of IHC staining may now be incorporated to enhance the detection rate of otherwise occult micrometastases.

Although numerous well-designed retrospective studies have suggested the negative impact for micrometastatic diseases, the significance of micrometastatic cancer in the SLN is as yet undetermined due to a lack of meaningful follow-up. However, as previously described with melanoma, there may be significant impact on prognosis and enhanced ability to preclude false-negative evaluations by careful analysis of the SLN. Whereas the routine use of SLN biopsy was incorporated into our practice in

1994, we believe that will likely require a five-year median follow-up time of sufficient numbers of patients to adequately address this important issue. In light of the number of cases of micrometastatic disease detected thus far using the SLN biopsy technique, it is clear that the significance of these findings has to be determined in prospective, randomized trials. Current trials underway, such as the American College of Surgeons Breast Lymphatic Mapping Trial and the Moffitt Cancer Center/Department of Defense Trial, will attempt to address the significance of micrometastatic disease detected in the SLN.

References

1. Gershenwald JE, Colome MI, Thompson W, et al, et al. Patterns of recurrence following a negative sentinel lymph node biopsy in 423 patients with stage I and II melanoma. *J Clin Oncol*. 1998;17:2253-2260.
2. Krag D, Weaver DL, Ashikaga T, et al. The sentinel node in breast cancer: a multicenter validation study. *N Engl J Med*. 1998;339:941-946.
3. Veronesi U, Zurrada S, Galimberti V. Consequences of sentinel node in clinical decision making in breast cancer and prospects for future studies. *Eur J Surg Oncol*. 1998;24:93-95.
4. Heller R, Becker J, Wasselle J, et al. Detection of submicroscopic lymph node metastases in patients with melanoma. *Arch Surg*. 1991;126:1455-1460.
5. Wang X, Heller R, Van Voorhis N, et al. Detection of submicroscopic lymph node metastases with polymerase chain reaction in patients with malignant melanoma. *Ann Surg*. 1994;220:768-774.
6. Shivers SC, Wang X, Li W, et al. Molecular staging of malignant melanoma: correlation with clinical outcome. *JAMA*. 1998;280:1410-1415.
7. Prognostic importance of occult axillary lymph node micrometastases from breast cancers. International (Ludwig) Breast Cancer Study Group. *Lancet*. 1990;335:1565-1568.

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8. Prolonged disease-free survival after one course of perioperative adjuvant chemotherapy for node-negative breast cancer: the Ludwig Breast Cancer Study Group. *N Engl J Med.* 1989;320:491-496.
9. de Mascarel I, Bonichon F, Coindre JM, et al. Prognostic significance of breast cancer axillary lymph node micrometastases assessed by two special techniques: reevaluation with longer follow-up. *Br J Cancer.* 1992;66:523-527.
10. Wilkinson EJ, Hause LL, Hoffman RG, et al. Occult axillary lymph node metastases in invasive breast carcinoma: characteristics of the primary tumor and significance of the metastases. *Pathol Annu.* 1982;17(pt 2):67-91.
11. Friedman S, Bertin F, Mouriessse H, et al. Importance of tumor cells in axillary node sinus margins ("clandestine" metastases) discovered by serial sectioning in operable breast carcinoma. *Acta Oncol.* 1988;27:483-487.
12. Hainsworth PJ, Tjandra JJ, Stillwell RG, et al. Detection and significance of occult metastases in node-negative breast cancer. *Br J Surg.* 1993;80:459-463.
13. Fisher ER, Palekar A, Rockette H, et al. Pathologic findings from the National Surgical Adjuvant Breast Project (Protocol No. 4). V. Significance of axillary nodal micro- and macrometastases. *Cancer.* 1978;42:2032-2038.
14. Clayton F, Hopkins CL. Pathologic correlates of prognosis in lymph node-positive breast carcinomas. *Cancer.* 1993;71:1780-790.
15. Trojani M, de Mascarel I, Bonichon F, et al. Micrometastases to axillary lymph nodes from carcinoma of breast: detection by immunohistochemistry and prognostic significance. *Br J Cancer.* 1987;55:303-306.
16. Dowlatsaha K, Fan M, Bloom KJ, et al. Occult metastases in the sentinel lymph nodes of patients with early stage breast carcinoma: a preliminary study. *Cancer.* 1999;86:990-996.