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Periareolar Injection and the Sentinel Node in Breast Cancer

ABSTRACT & COMMENTARY

Synopsis: *A comparison between the standard peritumoral injection site and the periareolar site showed a possible advantage for the latter in identifying the sentinel lymph node in breast cancer. The technique may also be easier to perform.*

Source: Shimazu K, et al. *Surgery*. 2002;131:277-286.

THE DEVELOPMENT OF THE SENTINEL LYMPH NODE (SLN) technique has been a major advance in the area of cancer care. For breast cancer patients, the most widely accepted technique uses a peritumoral injection. Recently, a newer approach using a periareolar injection has been developed which offers potential advantages. This study from Japan reports on 2 separate protocols which will be referred to as study 1 and study 2.

Study 1 included 62 patients with T1-2 breast cancer whose SLN was identified by the peritumoral injection of blue dye into the parenchyma surrounding the tumor or into the wall of the biopsy cavity. After the SLN was identified, a complete axillary lymph node dissection (ALND) was performed in all patients. A SLN was "positive" if metastatic disease was demonstrated by either standard histology or immunohistochemistry after sectioning into 2 mm slices. Nonsentinel nodes were examined by a single representative section using routine histology only. A sentinel node was identified in 50 patients (81%), 17 (34%) of whom harbored metastatic disease. The SLN was the only positive node in 5 patients (29%). The false-negative rate was 5.5%.

Study 2 included 93 patients with T1-2 breast cancer whose SLN was identified using both blue dye and a radiotracer injection. In all 93 patients, the blue dye was injected using a peritumoral injection. The radiotracer injection, given the day before surgery, was peritumoral in 41 patients and periareolar in 52 patients. The periareolar injection was administered into 4 equally spaced periareolar locations, both intradermally and subdermally, with a total of 2 mL of 30-80 MBq of Tc-tin colloid. A complete ALND was performed only if: 1) the SLN could not be identified, 2) the tumor size was greater than 3 cm, or 3) the SLN was positive by frozen section.

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INSIDE

Compared with the standard peritumoral injection technique, the periareolar injection had a statistically significant advantage both for preoperative SLN identification by lymphoscintigraphy (90% vs 51%) as well as intraoperative SLN identification using the gamma probe (98% vs 85%).

COMMENT BY KENNETH W. KOTZ, MD

Shimazu and colleagues present data from 2 studies: performance of a standard SLN biopsy using only blue dye with a backup ALND in all patients ("study 1"), and a comparison between peritumoral and periareolar injection of radiotracer (study 2). Although not explicitly stated, it appeared that the 2 studies were performed concurrently rather than sequentially since patients with larger tumors "were preferentially enrolled" in study 1 where a backup ALND would always be performed. It should be emphasized that it is not stated whether the patients in study 2 were randomly assigned or not to 1 of the 2 arms.

In study 2, the periareolar injection site appeared superior to the standard peritumoral injection site. This might be expected due to the unique anatomy of the breast lymphatics. First, uptake of radiotracer in the areola is facilitated by the rich lymphatic network when compared with the breast parenchyma. Second, the direction of lymph flow is toward the subareolar lymphatic plexus and then toward the axillary nodes. This may account for the successful identification of SLNs in multifocal breast cancer.[1] Third, the injection can be either intradermal or subdermal due to the abundant number of connecting lymphatic vessels in the areola. Fourth, the sentinel node is not obscured by radioactivity from tumors in the upper, outer quadrant (shine-through phenomenon).

The learning curve for accurately identifying the SLN after a peritumoral injection is well known. Part of the challenge is correctly identifying the appropriate peritumoral site for injection, particularly for nonpalpable tumors. An advantage of the periareolar injection is its technical simplicity. Unlike study 1, where a learning curve was demonstrated, the rate of SLN localization did not improve during the performance of study 2.

Tc-tin colloid, available in Japan, has a larger particle size than Tc-sulfur colloid, available in the United States. Because the radioactivity is retained longer in the lymph node, detection with an intraoperative gamma probe can be performed the day after injection and, in addition, one minimizes the labeling of non-SLNs. A radiotracer with a larger particle size also passes into the lymphatic vessels with more difficulty. This may account for the low lymphoscintigraphic detection rates that have been reported with the use of large particle colloid when using the peritumoral injection site (51% in this study). This low SLN detection rate seems to be avoided with use of a periareolar injection (90% detection rate in this study) possibly due to the rich periareolar lymphatics which are more easily penetrated by the larger colloid preparation. Of note, a previous biopsy, particularly between the axilla and areola, reduced the ability to identify the sentinel node by lymphoscintigraphy after periareolar injection of a radiocolloid. Importantly, however, the SLN could still be identified intraoperatively with the gamma probe.

In study 2, 4 patients had extra-axillary localization of radiotracer, one of whom had an internal mammary node that contained metastatic disease. Because all 4 of these patients had positive axillary nodes, Shimazu et al hypothesize that the flow of lymph may be diverted in the presence of lymphatic vessel obstruction. In cases of clinically positive axillary nodes, they have observed (data not published) a higher rate of extra-axillary radiotracer accumulation when using the periareolar technique.

All in all, the study by Shimazu et al adds to the grow-

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ing body of literature regarding periareolar injection for the identification of the sentinel lymph node.[2-4] Regardless of technique, the optimal SLN identification rate should be > 90%, and the false-negative rate should be < 5%. Each surgeon should know their own false-negative rate, and should validate results before changing technique. However, it remains to be determined how best to perform a SLN biopsy in breast cancer patients. ■

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The Vermont Colorectal Cancer Project

ABSTRACT & COMMENTARY

Synopsis: *This study reports results of a statewide quality improvement project that was designed to evaluate prospectively gathered surgical and adjuvant treatment data for colorectal cancer patients. Surgeon compliance in reporting was estimated at 78% statewide. Among 364 elective cases, 82% were identified after presentation with symptoms, compared with only 18% identified by screening. Eighty-five percent of patients underwent resection for cure, and 100% of patients with stage III colon cancer and stage II and III rectal cancer were offered referral for adjuvant therapy. The most important finding of the study was the feasibility of statewide surgeon participation in the development of a database devoted to quality-of-care improvement for colorectal cancer patients.*

Source: Hyman N, et al. *Arch Surg*. 2002;137:413-416.

THE MEDICAL ESTABLISHMENT, THE LAY PRESS, AND legislators have focused increasingly on methods for assessing and improving the quality of health care in recent years, the latter 2 perhaps partially spurred by the Institute of Medicine's high-profile report on medical error released in 2000.[1] One response to the impetus for accurate assessment of quality of care has been development of a colorectal cancer patient database by the Vermont Chapter of the American College of Surgeons and the Vermont Program for Quality Health Care. The database contains patient-, tumor-, and procedure-associated information submitted by the operating surgeon at the time of the index procedure and pathology and short-term outcome data from a 30-day follow-up questionnaire. The primary goal of this study was to evaluate the feasibility of performing a quality-of-care study, specifically addressing the surgical care of colorectal cancer patients. A secondary goal was to describe cancer demographics and consider their relationship to current screening methods.

Between April 1999 and March 2001, 33 Vermont surgeons submitted initial operative data and 30-day follow-up questionnaires with pathology and perioperative morbidity/mortality data. Emergent cases were excluded, leaving 364 cases for analysis. According to Vermont Tumor Registry 2000 data, 670 colorectal cancer cases were expected over 2 years. After excluding the expected 30% of cases presenting emergently, 469 expected cases remain. Thus, surgeon compliance was estimated at 364/469 = 78%.

A substantial majority of patients (82%) were identified by presentation with symptoms, such as obstruction, bleeding per rectum, or change in bowel habits. The remaining patients were identified at screening. No information regarding whether the symptomatic patients had been previously screened or by what method was given.

Screening method accuracy is clearly linked to tumor site in the case of sigmoidoscopy vs. colonoscopy, and some evidence indicates that tumor site may have an effect on the accuracy of fecal occult blood studies.[2] Hyman and colleagues reported the frequency of tumor location in the right (36.6%), transverse (9.6%), descending (6.0%), and sigmoid colon (21.2%), and the rectum (26.6%). Again, no information regarding tumor site and previous screening or screening method was given.

Hyman et al reported an impressively high rate of appropriate treatment offered; 100% of patients underwent operation, 85% for cure, and 100% of patients were at least offered referral for adjuvant therapy. This contrasts a recent study reviewed by *Clinical Oncology Alert* in which 88% of rectal cancer patients underwent operation and 50-60% of those patients with stage II and III rectal cancer received adjuvant therapy,[3,4] the standard of care per 1990 NIH Consensus Conference recommendations.[5] Perioperative morbidity and mortality were 1.9% and 12.3%, both at the minimum of expected limits, indicating good short-term outcomes for patients undergoing care in this setting.

■ COMMENT BY ARDEN MORRIS, MD

By its broadest definition, studying "quality of care" is the goal of virtually every published investigation. In 1988, Donabedian described a framework for this con-

cept consisting of 1) structure, the attributes of the setting in which care occurs; 2) process, what is actually done in giving and receiving care; and 3) outcome, the effects of care on the health status of patients and populations.[6] He argued that a meaningful quality-of-care study mandated examination of each of these major components and the links between them. Surgical care for oncologic disease is an especially worthy arena for such study, given that surgical resection forms the foundation of care for most solid tumors, hard data regarding short-term outcomes is readily available, and the incidence of solid tumors remains high.

Hyman et al have begun this process by evaluating the surgical care of colorectal cancer in patients in Vermont. They are to be commended for developing one of the first surgeon-driven, population-based, quality-of-care projects. The primary aim was to examine the feasibility of this endeavor. They achieved a 78% estimated compliance rate among surgeons and demonstrated impressive short-term results. Still, there are substantial gaps in the information reported.

Although the secondary aim of this study was to assess the implication of cancer demographics for screening, no information was given regarding screening resources available, or even patient resources such as insurance type. They appropriately draw the only conclusion allowed by the data, which is that colorectal tumor sites appear to be migrating more proximally, furthering the case for screening by colonoscopy. This may be an arising biological imperative, but implementation of recommendations won't occur without resources (or, as implied by Donabedian's framework, Process depends on Structure).

Process, the second construct of quality of care, is addressed by describing the types of operations performed. However, because the point of entry for this study was performance of elective operation, no denominator is available to determine the frequency of appropriate or even any operation performed. Furthermore, "use of adjuvant therapy" is listed as a main outcome measure but the only information given is that all patients were offered referral for adjuvant therapy. Ideally, information about adequacy of adjuvant therapy should be supplied, although most database studies simply report a dichotomous variable for any adjuvant therapy received. In this study, the reported 100% "use of adjuvant therapy" is misleading.

Outcome, Donabedian's third construct, is the most thoroughly explored. Hyman et al describe short-term surgical morbidity (for specific complications) and mortality, with excellent results compared to the published literature. They acknowledge the absence of more meaningful long-term health status outcomes but clearly plan to continue gathering applicable data on ascertained cases. Cost information and patient utility information could round out this section of the overall study, and would be interesting to follow in the future. ■

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A Balloon Catheter for Partial Breast Intracavitary Brachytherapy

ABSTRACT & COMMENTARY

Synopsis: *Breast brachytherapy has been practiced for nearly 100 years, but its modern day use is limited to a few diehard radiation oncologists who have organized phase I/II trials in their own institutions. Based on promising early data from patients treated with a newly FDA-approved breast brachytherapy device, and on forthcoming RTOG toxicity data to be presented this fall, it appears that breast brachytherapy may become more popular in the near future. This study from William Beaumont Hospital published their experience with a dozen patients treated with the new applicator. They presented clinical observations and described dosimetry characteristics and considerations that will prove useful when deciding whether to offer this modality to our patients.*

Source: Edmundson GK, et al. *Int J Radiat Oncol Biol Phys*. 2002;52:1132-1139.

While breast brachytherapy has been practiced and written about for nearly a century, external beam radiotherapy following lumpectomy remains the standard. Though Janeway reported on interstitial radiotherapy for operable breast cancer in lieu of mastectomy in 1917, very few physicians have

adopted the procedure. Today's typical technique of inserting needles into the breast tissue surrounding a resection cavity varies little from the way brachytherapy was performed in Janeway's time. The main improvements have been computerization and image guidance. In spite of the fairly static nature of the basic technology, favorable data on adjuvant interstitial brachytherapy as a sole modality following breast-conserving surgery have begun to emerge as the technique has been revisited. This has attracted interest in the radiation oncology community. Most recently, new data from implementation of an innovative intracavitary applicator look promising.[1-3] If ongoing interstitial brachytherapy studies indicate that breast brachytherapy is efficacious in selected patients, then the new intracavitary applicator may supplant the older interstitial needles as the instrument of choice.

Edmundson and associates conducted a phase I trial testing safety, reliability, and dosimetric characteristics from June 2000 through May 2001 involving 12 patients in 9 hospitals. All 12 patients had T1N0 lesions with negative surgical margins, and all were implanted with a silicone balloon catheter at the time of their breast resection. The prescribed dose to the resection bed at 1 cm from the surface of the balloon was 3.4 Gy b.i.d × 10 = 34 Gy in 5 days. Treatments were commenced after the final pathology report was ready, usually postoperative day 2-3. Treatment was administered by attaching the balloon catheter to a standard high-dose rate brachytherapy unit containing an iridium-192 source. Eight patients were treated per protocol. Problems causing removal of the device in 4 patients included air pockets adjacent to the balloon, balloon asymmetry, and balloon puncture. At the conclusion of the therapy, the balloon was removed by the radiation oncologist after it was deflated. One patient developed moist changes from treatment, and the rest did well.

Edmundson et al concluded that, in comparison to historical controls, the new system provided better coverage of the target volume, ie, the resection cavity, and was more reproducible than interstitial brachytherapy. Critical issues discussed were the mandatory > 5 mm distance between the balloon and the skin surface, and the size limit of < 5 cm for the resection cavity. The former is necessary to prevent untoward reactions on the skin, and the latter maintains the overall treatment time to a reasonable length while keeping exposure to the heart and lungs low. Strict adherence to RTOG 95-17 protocol guidelines was emphasized several times throughout the paper. The main thrust of those guidelines is the careful monitoring of dosimetry parameters, most easily accomplished with image guidance.

COMMENT BY EDWARD J. KAPLAN, MD

If partial breast irradiation is shown to be efficacious in certain circumstances, then breast brachytherapy might enjoy some of the rising popularity that prostate brachytherapy has commanded over the last 10 years. This would be particularly true given the short learning curve that seems to be associated with the new balloon catheter system. Most radiation oncologists have never attempted breast brachytherapy, and a simple, effective tool would certainly make us more prone to trying it. Although the device has been approved for use by the FDA, the American Brachytherapy Society (ABS) still considers it to be investigational. In fact, it is so new that the just-published ABS guidelines for breast brachytherapy omit the intracavitary brachytherapy approach altogether.[4]

There are a host of potential advantages of a 5-day intracavitary brachytherapy program as the sole adjuvant radiotherapeutic treatment following lumpectomy. These include conformation of the radiation to the resection cavity rather than treatment of the entire breast, improvement of patient quality of life based on a shorter treatment schedule, simplification of treatment, elimination of logistical issues involving integration of chemotherapy and radiotherapy, increased willingness of women to undergo breast conservation because of the more convenient schedule, and the possibility of treating second primary ipsilateral breast tumors without fear of overlapping previously irradiated tissue.

Exclusion criteria were mentioned by Edmundson et al. These included resection cavities larger than 6 cm, T3-4 lesions, multifocality, positive margins, more than 4 involved lymph nodes, and intraductal histology. It appears that these are an initial set of empiric guidelines since no rationale was offered.

There has never been a randomized trial comparing external beam RT to brachytherapy alone in breast cancer. RTOG 95-17 is a phase I/II trial that was closed in March 2000 after accruing 99 patients who received interstitial breast brachytherapy as a sole modality post lumpectomy. Forty-five patients were treated with low-dose rate therapy, and 34 received the same HDR schedule used by the William Beaumont group. Toxicity data are scheduled to be presented at the upcoming ASTRO meeting in October 2002. It is anticipated that RTOG 95-17 will be followed by a phase III trial.

Aside from the question whether or not irradiation of most of the breast can be omitted in any cases following lumpectomy, there are other interesting points associated with use of an intracavitary system. For example, it is

not known exactly how much margin around the resection cavity is actually being treated since inflation of the balloon causes some amount of breast compression. Will the device eliminate postoperative seromas, and can it cause seeding of the incision line? Breast tissue tolerance to brachytherapy using this entirely new system is not known, and fat necrosis along with telangiectasias or worse may be important. Should the system be used as an up-front boost rather than as sole therapy in some or all cases?

One would hope that a system like that described by Edmundson et al can be shown to offer clinical benefit to our patients, given its easy deployment and use. As always, careful planning and measurements are essential to success. I am sure we will be hearing and reading much more about this technique in the months and years ahead. ■

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Imatinib Mesylate (Gleevec®) for CML Blast Crisis

ABSTRACTS & COMMENTARY

Synopsis: *Chronic myelogenous leukemia, when it evolves beyond the accelerated phase into blast crisis, becomes refractory to treatment and meaningful responses are few. In 2 recently published reports of phase II studies of imatinib mesylate (Gleevec®) treatment of blast crisis, response rates were 50% or more in each. Furthermore, a small percentage in each study achieved a complete cytogenetic response. Nonetheless, median survival, even for those with responsive disease, remained less than 1 year. They speculate that combinations including Gleevec® and cytotoxic chemotherapy would be a worthy next step in determining optimal management of this difficult malignancy.*

Sources: Sawyers CL, et al. *Blood*. 2002;99:3530-3539; Kantarjian HM, et al. *Blood*. 2002;99:3547-3553; Goldman J. *Blood*. 2002;99:3491-3492.

DESPITE RECENT REMARKABLE ADVANCES IN THE management of chronic myelogenous leukemia (CML) during the early, chronic phase, when the disease advances to the more advanced phases, treatment successes remain few. There is no standard therapy at this point for blast crisis and treatment has been typically what is used for acute leukemia, including allogeneic bone marrow transplant. Response rates remain low and median survival is 3-6 months.[1]

In the current issue of *Blood*, there are 2 papers that report the results of phase II trials of Imatinib mesylate (STI571, Gleevec®) for patients in CML blast crisis. Although only modest improvements in patient survival were observed, there were impressive response rates, more than previously reported for combination chemotherapy.

Sawyers and colleagues describe the results of an international, multi-institutional phase II study in which 260 patients with myeloid-lineage, accelerated phase or blast crisis CML were enrolled. Of these, 239 were confirmed to have myeloid blast crisis (> 30% myeloid blasts in the marrow). Patients were treated with imatinib in daily oral doses of 400 mg or 600 mg and hematologic responses were observed in 52% and sustained hematologic responses (lasting 4 weeks) in 31%, including complete hematologic responses in 8%. For patients with sustained response, the estimated median survival was 10 months and overall median survival was 6.9 months. Nonhematologic adverse events were frequent, but generally mild or moderate.

The second report by Kantarjian and colleagues was that of a single institution's (M.D. Anderson, Houston, Tex) experience treating CML blast crisis of both myeloid (n = 65) and lymphoid (n = 10) lineage. Doses of imatinib varied from 300 mg to 1000 mg per day.

Similar to the multi-institutional study mentioned above, the overall objective response rate was 52% (39 or 75). The cytogenetic response rate was 16% (12 patients) with 5 patients having complete cytogenetic response. The overall median survival was 6.5 months and the estimated 1-year survival, 22%. Kantarjian et al compared these results to historical controls, also treated at M.D. Anderson, mostly with cytarabine combinations and found imatinib to be both less toxic and more effective.

COMMENT BY WILLIAM B. ERSHLER, MD

The Philadelphia chromosome (Ph) is the hallmark of CML and it is a translocation of fragments of chromosome 9 and 22 resulting in the production of the Bcr-Abl fusion protein (p210) which is a constitutively active tyrosine kinase that mediates cellular transformation. The activation of p210 is causally related to the development of CML,[2] but progression to the more advanced stages is thought to depend on the develop-

ment of additional genetic changes, leading to loss of differentiation and a more problematic clinical picture. Thus, as Goldman points out in an accompanying editorial, the impressive responses observed in both studies were contrary to expectations and indicative of either a sustained importance of the Bcr fusion protein despite the accumulation of additional genetic damage, or the broader range of inhibitory activity of this previously considered, highly selective agent.

However, by whatever explanation, imatinib must now be considered an effective (perhaps the most effective) treatment for CML blast crisis. Yet, despite the impressive response rates, survival was budged only minimally. Hopefully, future trials will combine this agent with others to provide a more meaningful enhancement of survival. Also, it remains to be seen whether those treated with imatinib during chronic phase, will benefit from increased dosing or altered schedule when the blast crisis occurs. This, of course, has become a highly relevant question in light of the very common use of this agent early in the course of CML. In fact, even today, it is unlikely that patients will have progressed to blast crisis without an earlier treatment course with Gleevec®. ■

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CME Questions

27. Patients felt to be appropriate for breast brachytherapy include those with:
a. negative surgical margins.
b. invasive histology.
c. unifocal lesions.
d. All of the above

28. Intracavitary breast brachytherapy:
a. has been around for years.
b. does not appear to offer an advantage over interstitial brachytherapy.
c. is difficult to master.
d. may become routine in the future.

29. Which of the following is *false*?
a. The direction of lymph flow is toward the subareolar lymphatic plexus and then toward the axillary nodes.
b. The "shine through phenomenon" is most likely to occur with cancers in the upper outer quadrant.
c. A radiotracer with a larger particle size passes into lymphatic vessels with more difficulty.
d. Multifocal/multicentric breast cancer is never amenable to a sentinel lymph node biopsy.

30. In evaluating complete quality of care, the main categories to measure are:
a. patient preferences, health status, and cost-effectiveness.

b. structure, process, and outcome.
c. structure, process, outcome, and cost.
d. morbidity, mortality, and cost.

31. The best overall cancer screening method for the entire colon is:
a. fecal occult blood test.
b. sigmoidoscopy.
c. colonoscopy.
d. remains undetermined.

32. The most thorough overall screening method for the entire colon is:
a. fecal occult blood test.
b. sigmoidoscopy.
c. colonoscopy.
d. remains undetermined.

33. Imatinib (Gleevec®) treatment of chronic myelogenous leukemia has recently been shown to:
a. produce a 50% or greater response rate and remarkably prolong survival in patients with blast crisis.
b. produce a 20% overall response rate and have no effect on survival in patients with myeloid blast crisis.
c. produce a 50% or greater overall response rate but provide only a modest survival benefit when compared with patients treated with standard cytarabine-based regimens.
d. produce a 60% overall response rate and enhance median survival to greater than 2 years for patients with CML in blast crisis.

In Future Issues:

Prednisone Myeloma Remission Maintenance