

LETTERS TO THE EDITOR

LACTATION AFTER CONSERVATIVE TREATMENT FOR BREAST CANCER

To the Editor: There is an increasing number of patients who receive conservative treatment for early-stage breast cancer (1). Local and regional control, disease-free survival, and survival rates in women who receive conservative treatment are similar (if not better) than in women who undergo radical mastectomy (2). To increase the probability of cure, women are now encouraged to have periodic check-ups so tumors can be discovered in the very early stage of disease.

At the same time, however, the proportion of young patients with breast cancer is rising. Factors that must be considered in premenopausal patients treated with conservative therapy include the potential for them to become pregnant and breastfeed. However, there is scant information on this in the literature. We therefore report one experience in a young woman with breast cancer.

In January 1995, a 25-year-old nullipara woman with no noteworthy pathologic antecedents visited her gynecologist, who discovered a 23-mm nodule in the upper outer quadrant of her right breast 2 cm from the areola. Bilateral mammography and ultrasonography with fine-needle biopsy of the nodule for cytologic studies were performed preoperatively, and the findings indicated mammary adenocarcinoma. The study for distant metastasis was negative. On February 21, 1995, lumpectomy was performed via a periareolar incision, together with axillary lymphadenectomy. Pathologic studies revealed infiltrating grade II ductal adenocarcinoma without multifocality and a 3-mm tumor-free margin. Lymphoplasmic cell infiltrates, vascular invasion, and an extensive intraductal component were not found. The tumor was negative for the hormonal receptors for estrogen and progesterone, as well as for the p53 gene. The tumor was aneuploid, and S-phase was not determined. None of the 19 axillary lymph nodes excised were positive for disease.

External-beam radiotherapy of the right breast was initiated on March 2, 1995. A dose of 5,040 cGy was administered to the right breast in 28 fractions of 180 cGy each over a 5.5-week period via opposing tangential fields of ⁶⁰Co. On May 4, 6, and 8, the tumor site, including the surgical scar and a safety margin of 4 cm, received a boost dose. For this, ¹⁹²Ir high-dose rate (HDR) interstitial brachytherapy was used. To perform this treatment, four needles with an active length of 75 mm were implanted, and plastic tubes were then inserted and left in place during the entire course of treatment. A total dose of 2,700 cGy to the 85% reference isodose, with geometrical optimization of the dwell times was given in 9 fractions of 300 cGy each, three times every day, spaced 1 day apart. The patient tolerated

the treatment well, without any complications. No adjuvant treatment was administered.

All of the follow-up findings were correct, with no significant side effects or relapses, and the patient was deemed free of disease. In October 1997, the patient became pregnant, and gave birth on July 5, 1998, to a 3,670-g boy after an uneventful full-term pregnancy.

The patient wanted to breastfeed her infant. After delivering, the patient's untreated breast showed colostrum within 24 h. The treated breast, however, did not show any milk secretion until 72 h had passed. The nipple on the left side erected with more difficulty than the nipple of the untreated breast, and the child had less tendency to remain next to the nipple of the untreated breast. During lactation, the treated breast did not enlarge significantly, while the right breast showed the appropriate changes; hence, there was marked breast asymmetry (Fig. 1). The woman breastfed with both breasts for 6 weeks without problems. In the second week of lactation, a 5-ml sample of milk was obtained from both breasts for a biochemical assay to identify any possible differences between the two breasts. Table 1 compares the values found with those described for a previous case reported in 1986 in a patient who is currently free of disease (3). In February 1999, examination for local recurrence or distant metastases showed that our patient remained free of disease.

In the literature, there are only four published cases of patients who underwent conservative treatment for breast cancer who were able to nurse from the treated breast (4–7) and some others who were unable to breastfeed (8–10). We report the first case of breastfeeding in a patient who received HDR brachytherapy.

This case illustrates that an HDR brachytherapy boost does not seem to increase the probability of long-term side effects in the patient, if the treatment is done in a properly fractionated fashion. In our experience in more than 500 breast cancer patients treated with an HDR boost, no late side effects have been observed in those who received 500 cGy or less per fraction. HDR brachytherapy has important advantages from the point of view of radioprotection and treatment planning; the only disadvantage is that the treatment must be fractionated. Given the high local control rate and low rate of long-term side effects in our clinical series of 500 patients,



Fig. 1. Patient at 4 weeks after lactation. Note the significant asymmetry between the right (treated) and left (untreated) breasts.

Table 1. Comparison of characteristics of milk from both breasts obtained during the second week of lactation in our patient and a previously reported case (3)

Characteristics	Actual case		Previous case	
	Treated breast	Untreated breast	Treated breast	Untreated breast
Density	1.037	1.044	1.035	1.042
Na (mmol/l)	28.7	8.5	29.3	8.2
K (mmol/l)	12.2	14.4	12.8	14.3
Phosphates (mg/dl)	2.4	6.2	2.6	6.3
Triglycerides (mg/dl)	1531.0	3578.0	1548.0	3619.0
LDH (U/dl)	269.0	344.0	274.0	353.0
GOT (U/dl)	35.0	44.0	34.0	51.0
GPT (U/dl)	54.0	66.0	49.0	85.0
Alkaline phosphate (IU/dl)	92.0	83.0	89.0	52.0
Albumin (g/dl)	1.8	1.6	1.3	1.56

we believe that HDR brachytherapy is the treatment of choice for delivering a boost to the tumor bed.

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1. Fernández-Cid A. Tratamiento conservador del cáncer de mama. *Med Clin (Barc)* 1989;93:611–612.
2. Guix B, Lejárcegui JA, Guix R, *et al.* Tratamiento de los estadios I y II del cáncer de mama mediante cirugía conservadora e irradiación con sobreimpresión del lecho tumoral mediante Iridio 192. Experiencia en 92 pacientes seguidas 4 años. *Med Clin (Barc)* 1987;88:481–485.
3. Guix B, Lejárcegui JA, García J, *et al.* Lactancia por la mama tratada tras tratamiento conservador del cáncer mamario. *Rev Senología y Patol Mam* 1991;4:39–42.
4. David FC. Lactation following primary radiation therapy for carcinoma of the breast. *Int J Radiat Oncol Biol Phys* 1985;11:1425.
5. Findlay PA, Gorrell CR, D'Angelo T, *et al.* Lactation after breast radiation. *Int J Radiat Oncol Biol Phys* 1988;15:511–512.
6. Green JP. Post-irradiation lactation. *Int J Radiat Oncol Biol Phys* 1989;17:244.
7. Ulmer HU. Lactation after conservative therapy of breast cancer? *Int J Radiat Oncol Biol Phys* 1988;15:512.
8. Burns PE. Absence of lactation in a previously radiated breast. *Int J Radiat Oncol Biol Phys* 1987;13:1603–1604.
9. Rostom AY. Failure of lactation following radiotherapy for breast cancer. *Int J Radiat Oncol Biol Phys* 1988;15:511.
10. Rostom AY, O'Cathail S. Failure of lactation following radiotherapy for breast cancer. *Lancet* 1986;1:163–164.

NON-SMALL CELL LUNG TUMORS REPOPULATE RAPIDLY DURING RADIATION THERAPY

To the Editor: This letter points out that an estimate of repopulation rate during radiotherapy of non-small cell lung cancer (NSCLC) can be obtained from RTOG data published in usefully full detail by Cox *et al.* in 1993 (1) and foreshadowed in 1992 (2). The present estimate cannot be as satisfactory as a regression analysis where rate coefficients could be determined (3), but does suggest an important point. This new estimate of rate of loss of survival probability in NSCLC tumors is approximately as fast as for the well-established rate of loss of local control with treatment prolongation in head and neck tumors.

A markedly adverse association with survival was demonstrated if delays exceeded 5 days beyond planned treatment duration (1). The effect was limited to patients receiving at least 69.6 Gy (as 1.2 Gy twice daily). In 397 such patients the 1-year and 3-year survivals were stated to be 56% and 17% without delays, vs. 37% and 1% for patients with delays ($p = 0.0001$). These figures show a loss of survival probability of 19% and 16% at 1 and 3 years respectively for average delays greater than 5 days, with more detail in the published tables (1). The effect was marked in patients with none or only one unfavorable prognostic factor (unfavorable factors were KPS < 90, weight loss > 5%, nodal metastases $N > 3$). For delays of more than 5 days, patients with a reasonable probability of survival, by virtue of high dose and good prognostic factors, appeared to be losing local control significantly, resulting in a survival decrement of between 8 and 25%. (Tables 3 and 4 in Reference 1; see Table 1 accompanying this letter).

Table 2 in the 1993 paper by Cox *et al.* lists the number of patients experiencing defined delays of 5–9, 10–13, and ≥ 14 days as 31, 15, and 24 respectively, out of the 397 mentioned above. A median delay of 11 days can be calculated (three-tenths of the way from 10 to 14 days). No precise average delay can be obtained mainly because of the open-ended bin for ≥ 14 days. However, a weighted average delay of 10.7, 12.4, or 14.2 days can be computed, depending on whether the average of the ≥ 14 day bin is assumed to be 15, 20, or even 25 days longer than the planned treatment time.

Tables 3 and 4 in the same paper (1) list the percentages of patients surviving 1, 2, 3, and 5 years in two categories, either with none or just one unfavorable prognostic factor. For the readers' convenience, our Table 1 summarizes the pertinent data. The median reduction of survival probab-

Table 1. Survival with and without delays of 5 or more days, in patients receiving at least 69.6 Gy, from Tables 3 and 4 in Ref. 1

	Number		Survival (%)			
	Treated	Dead	1 yr	2 yr	3 yr	5 yr
A. Patients without unfavorable features*						
No delays	179	152	64%	33%	24%	15%
Delays	21	20	52%	14%	5%	0%
Difference (loss of survival)			12%	19%	19%	$\geq 15\%$
B. Patients with 1 unfavorable feature*						
No delays	136	122	53%	22%	13%	8%
Delays	29	29	28%	3%	0%	0%
Difference			25%	19%	$\geq 13\%$	$\geq 8\%$

*Unfavorable feature = KPS < 90, wt. loss > 5%, N3.

ity (associated with any delays > 5 days) is 19%. At the 1-year follow-up time the loss in survival was 12% for the favorable patients and 25% for the less favorable category, averaging 18.5% loss at 1-year follow-up for all delays > 5 days.

The difference in 2-year survival among patients without unfavorable features is 33% – 14% = 19% with a 95% confidence interval of (3%, 35%), assuming few or no losses to follow-up before two years [this appears reasonable, judging from the Kaplan-Meier curves (1)]. The analogous difference among patients with one unfavorable feature is coincidentally also 19%, with a confidence interval of (10%, 28%). Dividing 19% by the range of weighted average delays of 10.7, 12.4, or 14.2 days obtained above yields loss rates at 2 years of ≥ 1.8 , 1.5, or 1.3% per day, depending on the actual average delay beyond 14 days. The loss rate at 3 years is consistent with this. The median rate of loss was 19%/11 days = 1.7% per day.

One comment that applies here, as well as to the original paper of Cox *et al.*, is that these numbers represent only associations of delays with clinical outcome. The reference by Cox *et al.* to “the effects of treatment interruptions” should not be taken to imply any proof of causality from these data, which arise from trials that were not randomized with respect to treatment delay. In view of this we shall consider more widely the relevant data from head and neck data below.

The uncertainty in actual delays is unwelcome, but enough information is available to demonstrate that the rate of loss of survival probability in these NSC lung tumors is similar to that in head and neck tumors, estimated in a recent review as an average of 1.66% per day loss of local control (4). Details of this estimate are given in the following two paragraphs.

It is well known that, for tumors of the upper aerodigestive tract, prolongation of radiotherapy leads to a relatively rapid loss of local control (5–13). It is noteworthy that the latest comprehensive review (4) finds the same rate of loss, and of the dose–time trade-off, as the earliest of the detailed analyses published (5–7). Several of the series reviewed since 1990 showed an improvement of local control with shortening, and a number of them were randomized trials. These two points counter the argument that bias in clinical selection was leading to an artefactual apparent loss of local control with prolongation. The best available interpretation is that the overall time factor for tumor outcome is due to proliferation of clonogens in the tumor, at least after 3 or 4 weeks of radiotherapy (6, 8, 9, 14). The rates for head and neck tumors were, both in 1983 (5), and as reviewed recently (4, 12), an average loss of local control of 1 to 2% per day and a dose–time trade-off of 0.4–0.8 Gy per day (normalized to 2 Gy fractions). These rates correspond to a clonogenic doubling time of 3 to 3.5 days (5–7, 12).

The recent analysis for the UK Royal College of Radiology (4) showed the average rate of loss in larynx/pharynx carcinomas to be 1.66% (absolute) of local control per day (95% CI 1.28–2.04). This is the weighted average of 15 references to five split-course and 10 intermittently interrupted series. The nine available dose–time trade-off rates averaged 0.61 Gy/day [95% CI = 0.54–0.68, although several individual determinations claimed confidence ranges as wide as 0.1 to 2.8 Gy/day (4, 9)]. This average value obviously compares remarkably well with the value of 0.61 Gy/day presented by Withers *et al.* in 1988 (6). Rates of loss of local control were slower in carcinoma of the cervix, skin, and prostate (4).

Recent evidence from Aarhus, Denmark (13) and Mount Vernon, London (15) has shown that poorly differentiated squamous cell tumors benefited less from accelerated radiotherapy than did well-differentiated tu-