D0929
A PROSPECTIVE STUDY OF PARTIAL BREAST ADJUVANT RADIATION THERAPY AFTER RESECTION OF BORDERLINE AND MALIGNANT PHYLLODES TUMORS

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1.0 INTRODUCTION

Phyllodes tumors of the breast are uncommon neoplasms which present in young women (median age 45 years). Phyllodes tumors have been characterized by the World Health Organization based on histologic features as benign, borderline or malignant (1,2). Diagnostic histologic features include the number of mitoses per high power field, presence of infiltrating tumor near the margins, and cellularity and degree of stromal atypia. This categorization predicts the tumor's metastatic potential fairly well: in one review 0.4%, 4.3% and 22% of patients with benign, borderline and malignant phyllodes tumors developed metastases (3).

According to recent SEER data, approximately 500 women are diagnosed with malignant phyllodes tumors in the US each year and about half of those patients are treated with breast conserving resections as the only therapy (4). We reviewed the literature to determine the rate of local recurrence after margin-negative breast conserving resection of borderline malignant and malignant phyllodes tumors (5). A total of 13 studies were identified. Local recurrences occurred in 37/124 (21%) patients. Twelve of fifty (24%) patients with borderline malignant tumors and 25/124 (20%) patients with malignant phyllodes tumors experienced a local recurrence. The median follow-up in these studies ranged from 3.1- 9 years. Of note, the vast majority of recurrences occurred within 2 years of surgery: the median time to recurrence was 24 months or less in all but one of these studies.

This local recurrence rate is unacceptably high, as there are multiple adverse consequences of in-breast recurrences. There is substantial psychological morbidity. There is cosmetic morbidity: patients with recurrent phyllodes tumors will require wide local re-excision or mastectomy. Furthermore, several studies have shown that local recurrence of phyllodes tumors is a strong predictor of metastatic spread (6-8). A multivariate analysis in one of these studies indicated that local recurrence of phyllodes tumors was associated with a significantly increased risk of death (8). Concern remains for the potential for local recurrences to metastasize, as was demonstrated in a recent meta-analysis of randomized prospective studies of patients with invasive breast cancer (9). In this study it was determined that for every 4 local recurrences that were avoided, one breast cancer death was prevented.

In 1998 we initiated a prospective single arm study (DMS 9801) to determine whether adjuvant radiation therapy after breast conserving resection of borderline and malignant

phyllodes tumors decreases the local recurrence rate (5). Forty six women were treated at 30 different institutions. The mean patient age was 49 years (18-76). Thirty patients (65%) had malignant phyllodes tumors, the rest were borderline malignant. The mean tumor diameter was 3.7 cm (0.8-11 cm). Eighteen patients had a negative margin on the first excision. The median size of the negative margin was 0.35 cm (range <0.1-2 cm). Twenty eight patients underwent a re-excision because of positive margins in the initial resection. Two patients died of metastatic phyllodes tumors. With a median follow-up of 56 months (range 12-129 months), none of the 46 patients developed a local recurrence (local recurrence rate zero (95% CI 0 - 8%)). We concluded that adjuvant radiation therapy decreased the local recurrence rate after breast conserving resections of phyllodes tumors.

A recent retrospective report from the Rare Cancer Network also provides strong support for the use of adjuvant radiation therapy after resection of phyllodes tumors (4). Of 159 patients with borderline or malignant phyllodes tumors, 109 were treated with breast conserving surgery and 50 underwent mastectomy. Thirty six received adjuvant radiation therapy. When all 159 patients were considered the percentage free of local recurrence at 10 years in the group that received radiation therapy was significantly better than the group that did not receive radiation therapy (86% vs 59%, p= 0.02). Of the 109 patients treated with breast conserving surgery, 11 underwent radiation therapy and 68% were free of local recurrence at 10 years compared to 54% of the 98 patients who underwent lumpectomy without radiation therapy. Of the 50 mastectomy patients, 25 underwent radiation therapy and 92% were free of local recurrence at 10 years, compared to 78% of the patients undergoing mastectomy without radiation therapy. While the trends in each of these subgroups favor radiation therapy, the differences were not statistically significant. In multivariate analysis the only favorable independent prognostic factor was the use of radiation therapy.

On the basis of the foregoing studies we have recommend adjuvant radiation therapy for all patients with malignant phyllodes tumors who undergo breast conserving resections. We feel that adjuvant radiation therapy is also indicated after breast conserving resection of patients with borderline malignant phyllodes tumors. Although the concern for the metastatic potential of a locally recurrent borderline phyllodes tumor is less than that for a locally recurrent malignant phyllodes tumor, borderline phyllodes tumors do metastasize in 2-4% of cases (3,4). Furthermore, it is well documented that recurrent phyllodes tumors can progress to a more malignant phenotype than that seen in the initial tumor (9-13). Finally, since borderline

malignant phyllodes tumors locally recur as frequently as malignant phyllodes tumors after margin negative resection, adjuvant radiation therapy can prevent the morbidity associated with the need for additional surgery in 20-25% of these patients.

New methods for delivering breast radiotherapy are being developed that allow radiation to be delivered solely to the area of the surgical resection site, termed partial breast radiation. The main advantage of partial breast radiation is that it simplifies treatment for the patient: radiation is delivered twice a day for 5 days, rather than 5 days per week for 6 weeks. The main concern is that partial breast irradiation might miss other sites of breast cancer in the ipsilateral breast. This is a significant concern for patients with invasive ductal or lobular carcinoma, where multicentric tumors may be present in 5 to 10% of patients. This concern was lessened by data from the NSABP-06 study, where patients were randomized to receive lumpectomy or lumpectomy plus radiation therapy. In this study the development of tumors "elsewhere" in the ipsilateral breast (away from the primary tumor site) was the same (3%) whether or not the patient received adjuvant radiation therapy (14). Indeed, evidence is accumulating from prospective studies that adjuvant partial breast irradiation after resection of invasive adenocarcinoma of the breast results in rates of local recurrence that are comparable to those seen after whole breast radiation therapy. The study with the longest follow-up utilized several brachytherapy catheters to radiate just the area around the surgical resection site in 120 patients undergoing breast conserving surgery (15). The local recurrence rate at 5 years was 1%, which is comparable to that achieved in patients undergoing whole breast radiation. The Mammosite® catheter has simplified the delivery of partial breast radiotherapy. This is a balloon catheter which can be easily inserted in the cavity left after breast conserving surgery. A radioactive source is placed in the center of the balloon to deliver radiation. A large registry of 1440 patients treated with partial breast radiation indicates that at 3 years of follow-up the local recurrence rate after breast conserving surgery and Mammosite® brachytherapy is very low: 1.6% (16). An alternative method of partial breast radiotherapy which is gaining in popularity is external beam partial breast radiation therapy. This technique does not require placement of a balloon catheter in the breast, but relies on careful dosimetry to focus external beam radiation to the area around the surgical site. Although there is only short follow-up data available for patients treated with external beam PBI, this technique has been used for greater than 70% of women treated with PBI on the NSABP B-39 protocol. Both Mammosite® and external beam partial breast radiation

therapy are currently being compared to whole breast radiation therapy in the prospective randomized study, NSABP-B39.

In contrast to patients with invasive carcinomas of the breast, it is very rare for patients to have multicentric phyllodes tumors. In our literature review all 37 recurrences seen in the 124 patients that had undergone margin negative breast conserving resections were at the site of the initial tumor resection. Therefore we hypothesize that adjuvant partial breast irradiation is likely to be as effective as whole breast radiation therapy after resection of malignant phyllodes tumors.

2.0 OBJECTIVES

2.1 The primary objective is to determine the local recurrence rate for patients with borderline or malignant phyllodes tumors treated with breast conserving resection with negative margins and adjuvant partial breast radiation therapy.

2.2 The secondary objective is to compare the local recurrence rate observed after partial breast radiation therapy with that observed in historical controls treated with whole breast radiation therapy after breast conserving resection with negative margins (study DMS 9801, ref 5).

2.3 Additional secondary objectives will be to observe the incidence of tumor development elsewhere in the breast and the rate of distant metastases.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.11 Histologic proof of phyllodes tumor of borderline or malignant grade, as first defined by Pietruszka and modified by Azzopardi and adopted by the World Health Organization (1,2,17):
Borderline malignant: 5-9 mitoses/10 HPF, pushing or infiltrating margins, 2+ (moderate) stromal cellularity and atypia.
Malignant: 10 or more mitoses / 10 HPF, predominantly infiltrating margins, usually 3+ (severe) stromal cellularity and atypia but occasionally 2+.

3.12 The tumor has been excised with a breast-conserving resection and there is no tumor seen at any of the margins of the resection.

3.13 No prior breast carcinoma or ductal carcinoma in situ in the ipsilateral breast. Patients with a local recurrence of a previously excised phyllodes tumor are eligible if the recurrence is in the area of the previous excision.

3.14. No history of irradiation of the ipsilateral breast.

3.15 No evidence of other areas worrisome for cancer on physical examination and mammography of the ipsilateral breast.

3.16 Age $\geq$18 years.

3.17 Informed consent

3.18 Documentation that either: 1) the patient's medical insurance company has certified that they will pay for the cost of radiation therapy treatments, or 2) a letter from the patient indicating that they explicitly understand the costs of radiation therapy and that the sponsor (Principal Investigator) of this study will not be held responsible for these costs.

3.2 Exclusion Criteria.

3.21 Histologically positive margins.

3.22 Breast carcinoma or ductal carcinoma in situ in the ipsilateral breast.

3.23 A history of irradiation to the ipsilateral breast.

3.24 Pregnancy. A urine pregnancy test will be performed on each fertile premenopausal female prior to entry into the study. Patients with childbearing potential must employ effective contraception during the radiation therapy.

3.25 A radiation planning CT scan which demonstrates a target lumpectomy cavity that is not clearly delineated or a target lumpectomy cavity/whole breast reference volume > 30%.

3.26 Unacceptable radiation therapy quality assurance parameters, as defined in Section 5.

4.0 PRE-TREATMENT EVALUATION

To register a patient, call the Clinical Research Coordinator for this protocol at the Office of Clinical Research at Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756. Pathology slides, and the information indicated in section 4.2, needs to be submitted. The Principal Investigator or his designee will determine whether a patient is eligible for enrollment on the protocol.

To discuss any aspect of the protocol, please contact the Principal Investigator, Dr. Richard Barth, Department of Surgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756 at 603-650-9479 (phone), 603-650-8608 (fax) or Richard.J.Barth.Jr.@Dartmouth.EDU.

4.1 Pathology Review

Representative slides from the resected tumor will be evaluated by Dr. Wendy Wells, Pathology, DHMC, for assignment of histologic grade. A report from the Department of Pathology at the institution where the resection was performed must include a determination as to whether negative margins were achieved, a measurement of the distance to the closest margin, and tumor size. Patients with initially positive margins who have been re-resected with negative margins will be eligible.

4.2 Pretreatment data to be submitted

Patient name
Patient birth date and age at diagnosis
History, noting presence or absence of prior breast surgery, irradiation and breast malignancies
Location of tumor in the breast and side affected (left/right)
Operative report from the tumor excision
Pathology report from the tumor excision, with information on margins and tumor size, as described in section 4.1
Bilateral mammogram report
Ultrasound report, if obtained
MRI report, if obtained.

Referring physician, surgeon, radiation oncologist and treating institution

5.0 RADIATION THERAPY

Radiation therapy will be administered in the vicinity of the center where the surgical resection was performed. Adjuvant radiation must start within 12 weeks of breast excision or re-excision. External beam partial breast radiation will be administered per guidelines used in the NSABP B-39/RTOG 0413 protocol.

5.1 PBI by 3D conformal external beam radiotherapy (3D-CRT)

5.1.1 Imaging

Treatment planning must be performed using a CT scan with less than or equal to 0.5cm slice thickness and extending superiorly from the mandible to below the inframammary fold inferiorly. The treatment planning scan should include the entire both lungs.

5.1.2 Target volumes

Lumpectomy cavity will be outlined based on visualization of the cavity on CT scan with or without the assistance of surgical clips.

Clinical Target Volume (CTV) is defined by expansion of the lumpectomy cavity by 15mm, but limited to 5mm of skin surface and will not include the chest wall and pectoralis muscle.

Planning Target Volume (PTV) accounts for treatment position uncertainty and will be defined as a 10mm expansion on the CTV.

PTV_EVAL excludes the expansion outside of the patient and the first 5mm of tissue under the skin and excludes chest wall, pectoralis muscle and lung.

5.1.3 Beam angles/treatment planning

Beam arrangements are at the discretion of the treating oncologist. 3, 4, or 5-filed non-coplanar beam arrangements are recommended. No electrons can be used. High-energy photons

can be used. No beams can be directed towards critical structures including heart, lung or contralateral breast. The PTV (not the PTV_EVAL) will be used to plan the beam apertures.

5.1.4 Dose prescription

A total dose of 38.5 Gy will be prescribed to the isocenter given in two fractions per day of 3.85 Gy for ten fractions with at least 6 hours between fractions. Treatment will be initiated within 12 weeks of surgery and completed within 10 days of the first fraction.

5.1.5 Dose limitations (as per NSABP B-39)

Univovled normal breast- <60% whole breast reference vol should receive >50% of prescribed dose (1925cGy) and <35% should receive prescribed dose.
Contralateral breast- <3% of prescribed dose (115cGy) to any point
Ipsilateral lung- <15% of the lung can receive 30% of prescribed dose (1155cGy)
Contralateral lung- <15% of the lung can receive 5% of the prescribed dose (192.5cGy)
Heart (right-sided lesions)- <5% should receive 5% of prescribed dose (192.5cGy)
Heart (left-sided lesions)- Volume receiving 5% of prescribed dose (192cGy) < 40%
Thyroid- max point dose 3% of prescribed dose (115cGy)

5.1.6 Treatment verification

Prior to delivery of the first treatment, portal films or images of each beam and an orthogonal pair will be obtained. An orthogonal pair film or image will again be obtained prior to the 5th treatment. Additional treatment verification films will be at the discretion of the local treating physician.

5.1.7 Plan evaluation

Dose volume histograms must confirm that 90% of the prescribed dose covers at least 90% of the PTV_EVAL. The maximum dose cannot exceed 120% of prescribed dose.

5.3 Radiation Therapy Quality Assurance

5.3.1 Physicians approved by RTOG for PBI

The RTOG has an approval process for radiation oncologists who are participating in NSABP B-39. This requires each investigator to submit 5 PBI plans for central review. If an investigator

has been RTOG approved for PBI, then plans will not have to be submitted to Dr. Jarvis prior to treatment on this protocol D0929.

5.3.2 Physicians not approved by RTOG for PBI

For radiation oncologists who have not been RTOG approved, the radiation treatment plan will be submitted to Dr. Jarvis for review and approval prior to initiation of radiation therapy. The following criteria will be used:

5.3.2.1 External Beam PBI

Dose volume histograms (DVHs) for the PTV_EVAL, designated critical structures and unspecified tissues will be judged as acceptable if:

1. DVH analysis of the target volume confirms 90% of the proscribed dose covers 90% of the PTV_EVAL.
2. Critical normal tissue DVHs are $\leq$ 5% of specified value.
3. Maximum dose does not exceed 120% of prescribed dose.
4. Dose to be delivered twice a day for a total of 10 treatments over a period of 5 to 10 days.

Dose volume histograms (DVHs) for the PTV_EVAL, designated critical structures and unspecified tissues will be judged as unacceptable if:

1. DVH analysis of the target volume confirms 90% of the proscribed dose covers $\leq$ 90% of the PTV_EVAL.
2. Critical normal tissue DVHs are $\geq$ 5% of specified value.
3. Maximum dose exceeds 120% of prescribed dose.
4. Dose to be delivered over a period of time > 10 days.

6.0 POST-THERAPY EVALUATION

All patients will be encouraged to perform monthly breast self examination and will be followed with physical exams of the affected breast by their surgeon or radiation oncologist. These physical exams should occur every 6 months (+/- 3 months) after the initial resection through year 5 (ie. at 6,12,18,24,30,36,42,48,54,and 60 months) and then every 12 months (+/- 3 months) years 5 through 10 (ie. 72, 84, 96,108 and 120 months). Mammograms will be obtained at 6 months (+/- 3 months) and 12 months (+/- 3 months) and then annually for 10 years after the initial resection. A 5 year minimum follow-up should detect almost all recurrences, since the

vast majority of local recurrences occur within 2 years of initial excision. Since it is possible that radiation therapy may delay, but not prevent recurrences, we propose a 10 year follow-up. Suspicious masses discovered by physical exam or by imaging studies will be biopsied per routine clinical care. Biopsy proven phyllodes tumor recurrences should be reported promptly to the Principal Investigator. Patients will be terminated from the study at the time of death or after 10 years of follow-up, whichever comes first.

7.0 DATA COLLECTION AND SAFETY MONITORING

Pre-therapy evaluation data, as detailed above, radiation therapy treatment data, as well as the results of post-therapy exams and imaging studies will be collected by the Office of Clinical Research at DHMC, and reviewed quarterly by the Principal Investigator (RJB). The NCCC Safety and Data Monitoring Committee will also monitor this protocol on a quarterly basis.

8.0 STATISTICAL CONSIDERATIONS

The primary objective of this study is to evaluate the in-breast recurrence rate of borderline and malignant phyllodes tumors treated with breast conserving resection and adjuvant partial breast radiation therapy. Based on our literature review, the in-breast recurrence rate after margin negative breast conserving resection alone is approximately 21 percent. A clinically meaningful improvement for the experimental therapy would be an in-breast recurrence rate of 5 percent or less.

The secondary objective is to compare the local recurrence rate observed after partial breast radiation therapy with that observed in historical controls treated with whole breast radiation therapy after breast conserving resection with negative margins (study DMS 9801, ref 5). This recurrence rate was zero (0/46 patients).

8.1 Statistical analysis

The rate of in-breast recurrence will be calculated with an exact binomial confidence interval. A binomial test (i.e., one sample proportion test) will be used to compare this rate to the rate of 21% determined from the literature for margin negative breast conserving resection alone. To address the secondary aim the rate from this study will be compared to the rate (0/46) obtained in the study using adjuvant whole breast radiation using a Fisher's exact test.

Additional analysis will include descriptive summaries of adverse events, time to recurrence and survival. Time to recurrence and survival will be estimated separately for the borderline and malignant tumor groups using the product limit method.

Sample Size and Power Considerations

A total sample of 50 patients will be enrolled and followed for recurrence. This yields sufficient power (i.e., 80%) to detect that adjuvant partial breast radiation is better than margin negative breast conserving resection alone, if indeed this adjuvant therapy reduces the rate to 6% or less, and the rate with resection alone is 21%. This calculation sets the type I error rate (α) at the usual 0.05. The 95% exact binomial confidence interval has an expected range of 1% to 15% if the actual rate is 5% (whereas it is 0% to 8% if the actual rate is 1%, and it is 4% to 22% if the actual rate is 10%). In comparison to the adjuvant whole breast radiation in which our prior study found no in-breast recurrences in 46 women, partial breast radiation will be identified as having a significantly higher rate if its actual rate is 15% or higher (assuming an α=0.5, and use of a Fisher exact test).

8.2 Patient Accrual

Based on SEER 17 data from 2000-2004, approximately 500 patients are diagnosed with malignant phyllodes tumors annually in the US (4). We will accrue to this study in the same manner we accrued to DMS 9801. An IRB approved recruitment website will be created which describes the study. We anticipate that patients will view the website and then contact the study Principal Investigator (PI) or a co-investigator. The trial will be described to the patient, and if the patient remains interested, the patient will be encouraged to have their physician contact the PI or co-investigator. Required information will be sent to the PI or co-investigator. All pathology slides will be reviewed by Dr. Wells and a determination of tumor grade will be made.

Some patients who are identified in this manner may be receiving their treatment from community oncologists who are not affiliated with an institution that has an IRB. In order for us to be able to accrue such patients to this study, the Dartmouth IRB has defined a mechanism whereby the treating institution can delegate review to the Dartmouth IRB under an IRB Authorization Agreement. Certain conditions must also be met if an institution does not have a Federalwide Assurance. These conditions are detailed in the following Table.

Definitions:
CPHS: The Committee for the Protection of Human Subjects at Dartmouth College
FWA: Federalwide Assurance. A formal, written agreement between a research institution and the federal government in which the research institution agrees to comply with the regulations for human subjects protection for federally funded research activities. The FWA and its associated IRBs are

registered with the Office for Human Research Protections (OHRP) at the U.S. Department of Health and Human Services (DHHS or HHS).
IRB: Institutional Review Board. A committee with a membership defined by the federal regulations for human subjects protection.

<table>
<tr><td colspan="3">Arrangements for review by an IRB for collaborative research that involves investigators 1) at another institution, and 2) who are engaged in the activities of the research project</td></tr>
<tr><td>FWA exist for collaborating institution?</td><td>Yes</td><td>No</td></tr>
<tr><td>IRB established for collaborating institution?

Yes</td><td>Local IRB review by the collaborating institution

Or

Delegation of review to CPHS under an IRB Authorization Agreement</td><td>Obtain FWA and rely on local IRB review

Or

1) Delegate review to the CPHS under an IRB Authorization Agreement, plus

2) Execute an individual investigator with attached reference documents, plus

3) Obtain a letter of support for the research activity from an official of the collaborating institution</td></tr>
<tr><td>No</td><td>Delegation of review to CPHS under an IRB Authorization Agreement</td><td>1) Execute an individual investigator agreement with attached reference documents, plus
2) Obtain a letter of support for the research activity from an official of the collaborating institution
Or
Obtain a FWA, plus delegate review
Or
Obtain a FWA, organize an IRB that performs reviews</td></tr>
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Notes:
1. If federal funding exists for the research project, an FWA needs to be obtained by each institution engaged in the research
2. The use of model consent form with an attachment containing local contact information is encouraged for multi-site research activities to reduce the administrative burden of review.

Documents which detail 1) the responsibilities of our IRB for review of another entity, 2) the IRB Authorization Agreement and 3) the Individual Investigator Agreement are included as addenda to this protocol (Addendum 1-3).

A consent form, personalized to the treating institution, will be drafted, based on a model consent form and signed by the research subject and treating physician.

This mechanism was used to accrue patients to our previous phyllodes study, DMS 9801. We were able to accrue, in this manner, 7 patients per year to DMS 9801. We anticipate that the publication of the results of DMS 9801 (ref 5) will stimulate interest in the treatment of phyllodes patients with radiation therapy and estimate that we will be able to accrue 12 patients per year. Thus this study should take 4 years to accrue the required sample size (50 patients. Accrual will be limited to patients in the US.

The study will be listed in Clinical Trials.gov.

9.0 RISK/BENEFIT STATEMENT

In an effort to decrease the local recurrence rate, while preserving the breast, we propose adding adjuvant radiation therapy to local excision. Partial breast radiation, if as effective as whole breast radiation therapy, is preferable for many patients because the duration of treatment is much shorter (5 days vs 6 weeks).

The risks of surgery plus external beam partial breast radiation therapy are:

1. Effects in 10% or more of patients: reddening of the skin during treatment and for several weeks following treatment, tanning of the breast skin which may be permanent, slightly smaller breast size or change in the way the breast looks, tiredness and weakness during treatment and for several weeks following treatment.
2. Effects in 3-9% of patients: peeling of the skin in the area treated with radiation, pain at the site of radiation.
3. Effects in < 1% of patients: cough, difficulty breathing, pericarditis, myocarditis, rib fracture.

Although there is a well documented risk of malignancy associated with exposure to radiation, we have searched the literature and are unaware of any studies which have demonstrated an increased risk of second malignancies in patients who have been treated with whole breast radiation therapy after breast conserving surgery. One study demonstrated that patients treated with whole breast radiation therapy did not have a significantly higher incidence of leukemia than patients treated with breast conserving surgery alone (18).

There is no evidence that treatment on this protocol will result in decreased survival from phyllodes tumors, even if the adjuvant radiation therapy is completely ineffective.

The benefits of being enrolled in this study are that the women will be treated with breast conservation, rather than mastectomy, and that they will receive adjuvant radiation therapy in a much shorter time frame than they would have if they were to receive whole breast radiation therapy.

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