Neoadjuvant Intracarotid Chemotherapy for Treatment of Advanced Adenocystic Carcinoma of the Lacrimal Gland

Melissa L. Meldrum, MD; David T. Tse, MD; Pasquale Benedetto, MD

Objective: To investigate a new chemotherapeutic regimen as an adjunct to the conventional surgical management of patients with advanced adenocystic carcinoma of the lacrimal gland.

Patients and Methods: Two patients with extensive adenocystic carcinoma of the lacrimal gland were treated with intracarotid cisplatin and intravenous doxorubicin hydrochloride prior to orbital exenteration. Postoperatively, the patients received 55 to 60 Gy of orbital irradiation, augmented by additional intravenous cisplatin and doxorubicin. Serial clinical and computed tomographic scan examinations were performed to monitor for evidence of recurrent disease.

Results: Tumor shrinkage was documented radiographically following this preoperative chemotherapy regimen, downstaging the disease in one case from intracranial involvement to a more surgically amenable intraorbital process. Tumor necrosis was confirmed in the exenteration specimen. Limited morbidity was experienced and both patients have achieved long-term survival to date of 9½ years (114 months) and 7½ years (94 months).

Conclusions: To our knowledge, this is the first report of the efficacy of neoadjuvant intracarotid chemotherapy in the treatment of an advanced adenocystic carcinoma of the lacrimal gland. The combination of cisplatin and doxorubicin and the methods of drug delivery may be factors contributory to the favorable response. The results of this new treatment regimen are encouraging and justify further investigation.


For editorial comment see page 372

A

N ADENOCYSTIC carci

toma of the lacrimal gland is the most common non-
lymphoid malignant tumor of the lacrimal gland, accounting for 25% to 30% of epithelial lacrimal gland tumors.1 Despite extensive surgery and radiation therapy, the prognosis for these patients remains grim, with survival of less than 50% at 5 years and a dismal 20% at 10 years.2 In an effort to improve survival, we incorporated neoadjuvant intracarotid chemotherapy combined with intravenous chemotherapy into the conventional treatment for this disease.

Chemotherapy has been used in the treatment of malignant epithelial tumors of the parotid and salivary glands, neoplasms that are of similar embryogenesis and biological behavior to an adenocystic carcinoma of the lacrimal gland. These tumors have demonstrated salutary response to cisplatin and doxorubicin therapy.3 Intra-arterial delivery of chemotherapy is an accepted treatment for extremity osteosarcoma,4 central nervous system tumors,5-10 primary and metastatic liver11-13 tumors, and breast cancer in selected patients.14-16 The major advantage of intra-arterial drug infusion is the ability to administer a dose of therapeutic agent to the area of involvement through an undisturbed vascular system, resulting in a better therapeutic index (Table 1). Depending on the target organ, the extraction rate may result in drug delivery that is many times higher than that achieved with standard intravenous therapy, and simultaneously associated with limited systemic toxic effects.7,17 In addition, neoadjuvant chemotherapy, chemotherapy given prior to the “primary” or definitive treatment, induces tumor cell necrosis and potentially minimizes dissemination of viable tumor cells during the subsequent surgical manipulation. Finally, induction chemotherapy may induce a reduction in tumor size, rendering the mass more amenable to surgery.

From the Departments of Ophthalmology (Drs Meldrum and Tse) and Medicine (Dr Benedetto), University of Miami School of Medicine, Miami, Fla. The authors, their families, their employers, and their business associates have no financial or proprietary interest in any product or company associated with any device, instrument, or drug mentioned in this article. The authors have not received any payment as consultants, reviewers, or evaluators of any of the devices, instruments, or drugs mentioned in this article.
PATIENTS AND METHODS

Two patients with biopsy-proven adenocystic carcinomas of the lacrimal gland were treated with the new chemotherapeutic protocol (Table 2).

Table 1. Glossary of Oncologic Terminology

<table>
<thead>
<tr>
<th>Therapeutic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>A therapeutic index is the ratio of drug dose producing toxic effects to the dose that produces response. Thus, therapy with a high therapeutic index implies that the “effective” or therapeutic dose can be given with limited or manageable toxic effects. A therapy with a low therapeutic index implies that effective therapy closely overlaps toxic therapy. By intra-arterial infusion, the dose of a drug delivered to the target tissue can be increased, while the systemic dose remains unchanged; this effectively increases the therapeutic index, while separating response from toxic effects.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extraction Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>The extraction rate of a drug in an organ is the ratio of the concentration of drug entering the target organ to the concentration exiting that organ. This rate is determined by the pharmacokinetics of the drug and organ. The higher the extraction rate, the greater the concentration of a drug in the target organ.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Area Under Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacological term describing the degree of drug exposure, expressed as drug concentration times time (plotted as drug concentration vs time on a graph).</td>
</tr>
</tbody>
</table>

Extrapolating from the use of regional infusion in other disease sites and the potential advantages described above, we treated 2 patients with locally advanced adenocystic carcinomas of the lacrimal gland using a new multidisciplinary treatment regimen of preoperative cytoreductive intracarotid chemotherapy and postoperative intravenous chemotherapy as an adjunct to conventional orbital exenteration and radiation therapy.

REPORT OF CASES

CASE 1

A 29-year-old man complained of a bulging right eye of 3 weeks’ duration. He denied any pain or double vision. Ocular examination findings were normal with the exception of limitation on upgaze of the right eye, mild ptosis with a decrease in levator function, 2-mm proptosis recorded by the Hertel measurement, and 2 mm of inferior globe displacement. Computed tomography scan examination disclosed an infiltrative lesion in the superior orbit with intracranial extension through the superior orbital fissure (Figure 1). A transcutaneous biopsy of the lesion revealed an adenocystic carcinoma of the lacrimal gland exhibiting combined basaloid and Swiss-cheese patterns. Given the extent of local disease involvement, tumor-free margins could not be assured even with a combined ophthalmic and radical neurosurgical resection. The rationales for selecting intraarterial neoadjuvant chemotherapy for this patient were (1) to induce tumor shrinkage in an attempt to bring the tumor margins to within the orbit, such that the entire lesion could be removed by orbital exenteration, and (2) to induce tumor cell necrosis to minimize dissemination of viable tumor cells during surgical manipulation.

Following a negative systemic evaluation, which included bone scan and computed tomographic scan of the chest and abdomen and appropriate baseline assessment of renal and cardiac function, the patient underwent 3 cycles of intracarotid cisplatin perfusion, combined with intravenous doxorubicin hydrochloride (Adriamycin) given at 3-week intervals. The cisplatin (100 mg/m²) was delivered via a catheter inserted through the ipsilateral femoral artery to the external carotid artery under angiographic control, selecting placement to achieve maximal distribution to the orbital structures using dominant tumor vessels as a guide. The dose of cisplatin was diluted in 500 mL of normal saline solution and delivered over 1 hour. Immediately following the intracarotid cisplatin infusion, the intracarotid catheter was removed and doxorubicin hydrochloride (25 mg/m² per day) was given intravenously. Additional doxorubicin hydrochloride doses (25 mg/m² per day) were given on each of the 2 subsequent days. Prior to chemotherapy, the patient was rehydrated overnight with 250 mL D5 0.45% NS to achieve a urine output greater than 150 mL/h. Hydration continued throughout the hospital stay. Antiemetic premedication included ondansetron hydrochloride.

Table 2. Treatment Regimen for Adenocystic Carcinoma of the Lacrimal Gland

1. After diagnosis and systemic workup to exclude distant metastases, the patient is admitted for neoadjuvant chemotherapy.
2. Pretreatment hydration to establish an adequate urine flow of at least 150 mL/h.
3. Placement of an intracarotid catheter into the selected arterial circulation of the tumor.
4. Cisplatin, 100 mg/m², diluted in 500 mL of normal saline is infused over approximately 60 minutes in the neuroradiology suite.
5. Maintain hydration for 48 hours.
6. Intravenous push doxorubicin hydrochloride 25 mg/m² daily for 3 days.
7. Neoadjuvant chemotherapy is given for at least 2 courses separated by 21 days, followed by serial orbital computed tomographic scans to assess “radiographic response.” Maximal response is defined as complete disappearance of the abnormality of stability between 2 imaging studies. A third cycle of chemotherapy may be given.
8. Three to 4 weeks after the last course of chemotherapy and following hematologic recovery (white blood cell count >2.5 × 10⁹/L with adequate polymorphonuclear leukocytes and a platelet count >100 × 10⁹/L), patient undergoes orbital exenteration.
9. Approximately 4 to 6 weeks after surgery, radiation therapy (55-60 Gy) is given in a standard daily fraction protocol.
10. Once each week, and just before receiving the radiation treatment for that day, cisplatin (20 mg/m²) is infused intravenously over 30 minutes as a radiation sensitizer. This treatment is preceded and followed by hydration in the outpatient clinic.
11. Two to 4 weeks after the completion of combined chemotherapy and radiation, intravenous cisplatin (100 mg/m²) and doxorubicin are given. After radiation, the dose of doxorubicin reduces to 20 mg/m² daily for 3 days. Chemotherapy administration is in the same manner as the preoperative therapy, but without the intra-arterial approach.
ride (Zofran), dexamethasone sodium phosphate, and lorazepam (Ativan). The patient remained hospitalized for the 3 days of treatment. Complications included initial segmental scalp hair loss in the region of perfusion, neutropenia, and fever. An episode of sepsis was encountered during intravenous chemotherapy treatment attributable to a dental abscess.

Computed tomography scans of the orbit (Figure 2) obtained 1 month after completion of the 3 cycles of intraarterial drug perfusion demonstrated shrinkage of the tumor, downstaging the disease from intracranial involvement to a more surgically amenable intraorbital process. Following hematologic recovery from chemotherapy, exenteration without bone removal was performed. A gross tumor was identifiable only within the orbit. Biopsy specimens of tissues in the region of the superior orbital fissure were free of tumor cells. The socket was lined with a split-thickness skin graft. Histopathologic examination of the main specimen contained areas of calcification and necrosis consistent with tumor lysis (Figure 3).

Approximately 6 weeks after exenteration and following complete healing of the socket, the patient began to receive fractionated radiation therapy to the orbit. A total of 55 Gy was delivered. Radiation therapy was given in concert with intravenous radiosensitizing cisplatin (20 mg/m²) once weekly on an outpatient basis. Four weeks following completion of radiation therapy, he was retreated with intravenous cisplatin (100 mg/m²) and doxorubicin (20 mg/m² daily for 3 days). A total of 6 cycles of chemotherapy were planned to eradicate any residual occult tumor cells, but patient fatigue precluded further treatment. He therefore received a total of 4 cycles of chemotherapy, 3 before and 1 after orbital exenteration. Subsequent serial clinical examinations and radiographic surveys have failed to demonstrate any evidence of recurrent local or distant disease 9 1/2 years (114 months) following primary surgery. The patient is completely functional and is comfortable wearing an exenteration prosthesis.

CASE 2

A 31-year-old man was seen with a several-year history of gradually decreasing vision in the right eye and a 6-month history of inferior globe displacement. He also noticed a firm mass in the supertemporal quadrant of the orbit. The patient denied any orbital discomfort but complained of diplopia on upgaze. Ocular examination re-
Results were remarkable for best-corrected visual acuity of 20/200 OD attributed to chorioretinal folds noted in the fundus. No afferent pupillary defect was present. There was limitation on upgaze on the right side. A firm, non-mobile mass was palpable in the supertemporal orbit asso- ciated with 3 mm of proptosis by Hertel measurement. An orbital computed tomographic scan (Figure 4) revealed a 2.5×3.0-cm extraconal mass and bony fossa remodeling. An excisional biopsy with en bloc removal of the mass via the lateral orbitotomy approach was performed. Pitting of the bone was noted at the time of tumor excision. Histopathologic examination disclosed a sclerosing cribriform pattern adenocystic carcinoma of the lacrimal gland with perineural infiltration and positive margins of the en bloc resection. Despite the fact that an excisional biopsy had been performed, it was believed that possible tumor residual, prominent perineural infiltration, and bony involvement justified the use of neoadjuvant intra-arterial chemotherapy prior to exenteration.

Following a negative systemic evaluation, the patient underwent neoadjuvant therapy with intracarotid cisplatin (100 mg/m²) and intravenous doxorubicin hydrochloride (25 mg/m² daily for 3 days) for 2 cycles delivered in an identical fashion as in case 1. A standard exenteration, combined with removal of the lateral orbital rim bone flap created during the initial lateral orbitotomy procedure, was done. A meshed split-thickness skin graft was placed in the orbit. Postoperatively, the patient received a total of 60 Gy of radiation therapy combined with radiosensitizing intravenous cisplatin (20 mg/m² per day). This regimen is administered once per week, prior to receiving radiation treatment for that day. Postradiation intravenous cisplatin (100 mg/m²) and doxorubicin hydrochloride (20 mg/m² daily for 3 days) were given every 3 to 4 weeks for 4 cycles. The patient received a total of 6 cycles of chemotherapy, 2 before and 4 after surgery. Adverse treatment effects experienced by this patient included hair loss, neutropenia, and fever. The patient has no evidence of recurrence 7½ years (94 months) following completion of treatment.

**COMMENT**

Adenocystic carcinoma of the lacrimal gland is a rare but devastating disease. The dismal prognosis is well documented. A study by Lee et al\(^\text{18}\) reported that 23 of 26 patients died of their disease. Forrest\(^\text{19}\) described a series of 20 patients, 11 of whom died of the disease within 8 years and 3 additional patients who died within 15 years. Of the remaining 6 patients, 2 died of causes unrelated to the lacrimal gland tumor and 2 had recurrent adenocystic carcinomas. The 2 patients who were disease-free had a follow-up period of only 2 and 4 years, respectively. In a more recent study, Wright et al\(^\text{20}\) reported a
lower mortality rate with 12 of 38 patients succumbing to the disease, 11 within 4 years and 1 at 13 years. In the group of survivors, 6 patients were alive with recurrent tumor. Of the 18 patients dead or alive with recurrent disease, 16 (89%) had recurrences within 1 year, 1 within 2 years, and 1 at 9 years. Of the 17 patients described as disease-free, 11 (65%) had less than 4 years of follow-up. Font and Gamel\(^1\) reported a series of 60 patients for whom follow-up information was available. Of these, 35 were dead of tumor, 3 were dead of other or unknown causes, 12 were alive with tumor, and 10 were without evidence of disease.

These studies thus document a recurrence rate of 55% to 88% generally within 5 to 6 years of diagnosis and significant mortality rate with standard local therapies. The series of Font and Gamel\(^1\) reported an actuarial survival rate of approximately 20% at 10 years regardless of treatment regimen that included local excision alone, exenteration, radiation alone, exenteration combined with radiation, and an unspecified chemotherapeutic protocol.

Henderson\(^{21}\) in an effort to further document and clarify long-term survival, surveyed experts in the field of orbital oncology. Of 26 respondents across the country, only 2 “possible cures” were identified, achieving 20 and 11.7 years disease-free survival from the initial treatment. The patient surviving 20 years was treated with exenteration and radiation therapy while the other patient underwent exenteration with removal of the roof and lateral wall of the orbit. No postoperative radiation was given in the latter case.

The poor survival rate has been attributed to the aggressive biological behavior of this tumor. The neoplasm tends to invade nerves and lymphatic channels, resulting in microscopic spread. Local recurrence is common, occurring in nearly half of patients within 2 years,\(^{20}\) with soft tissues or orbital bone as the most frequent sites. Bone and lung are common foci of distant metastases. An adenocystic lacrimal gland carcinoma also has a propensity for intracranial extension via the lacrimal nerve through the superior orbital fissure. Frequently, intracranial involvement is the principal cause of death.\(^{18,22}\)

Because an adenocystic carcinoma has a proclivity for microscopic, soft tissue, and bone infiltration, surgery alone does not routinely effect a cure in high proportion. Radiation therapy may “mop up” residual cancer cells but tissue penetration by radiation can be a limiting factor. Not surprisingly, exenteration, exenteration combined with radiation,\(^{2,16}\) and radical cranio-orbital resection\(^{20}\) have not resulted in improved survival.

Of cancer treatment options, chemotherapy has the greatest potential to eradicate occult metastatic disease. The experience of using chemotherapy in treating adenocystic carcinomas of the lacrimal gland is limited. A review of published data revealed that only 6 patients have received this form of therapy. In the retrospective study of Lee et al.\(^{28}\) 1 patient was treated with fluorouracil. Five patients received an unspecified chemotherapeutic regimen in a series reported by Font and Gamel.\(^1\) In the latter series, 4 patients died within 1 year and the fifth patient survived 3 years before succumbing to the disease. It is unclear whether chemotherapy was given alone or in conjunction with exenteration. Furthermore, our review of the literature failed to show that the combination of cisplatin and doxorubicin was ever used as a chemotherapy regimen. This drug combination was chosen because of the activity of these agents in tumors of similar embryogenesis, namely, salivary gland cancers.

Intra-arterial delivery of chemotherapy has been used for adenocystic carcinomas of the salivary gland\(^3\) and is a well-recognized and accepted method in treating a variety of tumors, including osteosarcoma,\(^4,6\) brain tumors,\(^7,10\) breast carcinoma,\(^14,16\) skin neoplasms,\(^24\) gastric cancer,\(^25,26\) invasive bladder cancers,\(^27\) head and neck carcinomas,\(^28,29\) and primary and metastatic liver cancers.\(^11-13\) The advantages of this method of delivery are 2-fold. First, a very high dose of drug is delivered to the target area.\(^7,12\) This potentially enhances tumor cell kills by increasing area-under-curve concentration and shifting the dose-response curve to the right. Second, systemic toxic effects may be limited if a high percentage of the drug is removed as it passes through the target capillary bed and the remainder is diluted in the systemic circulation. To optimize drug delivery, the intra-arterial treatment should be performed prior to surgery or radiation therapy before disruption of the tumor blood supply.

To be effective, intra-arterial perfusion must fulfill the following criteria: (1) the tumor area should be supplied by a single (or less optimally, predominant) feeding arterial vessel capable of cannulation, (2) the tumor must be chemosensitive, (3) the chemotherapeutic agent must be active in its injected state, and (4) there should be an enhanced therapeutic index and response compared with conventional systemic therapy.\(^35\)

The lacrimal gland receives its blood supply from both the internal and external carotid systems. The internal carotid artery gives off the ophthalmic artery, which then branches into the lacrimal artery. The lacrimal artery anastomoses with branches of the external carotid system in the orbit and within the eyelids. The carotid system is easily accessed via the ipsilateral femoral artery. Because delivery of chemotherapy via the internal carotid would lead to direct perfusion of the brain and potential untoward consequences, chemotherapy is given via the external carotid system and reaches the lacrimal artery via anastomotic branches in the orbit. Smaller catheters are now available that permit direct cannulation of the ophthalmic artery.

The choice of chemotherapeutic agents is derived from the experience in treating epithelial tumors of the parotid and salivary glands. Like adenocystic carcinomas of the lacrimal gland, epithelial tumors of the salivary glands are rare, rendering large chemotherapeutic trials difficult. However, intravenous cisplatin and doxorubicin have been used with success for these tumors.\(^3,34-37\) In vivo, cisplatin functions as an “alkylating agent,” producing interstrand and intranstand cross-links in DNA. Since the drug is not cell-cycle specific, it is effective against carcinomas with slower growth cycles, such as an adenocystic carcinoma. Suen and Johns\(^34\)
treated 53 patients with adenoid cystic carcinoma of the head and neck with cisplatin alone (45 patients) or in combination with other agents (8 patients). The overall response rate, defined as a reduction in tumor size, was 64%. Schramm and colleagues used cisplatin as a single agent in a pilot study and reported an overall response rate of 70%. Two other studies of recurrent salivary gland epithelial tumors revealed response rates of 36% (cisplatin combined with cyclophosphamide and pirarubicin) and 35% (cisplatin combined with doxorubicin and fluorouracil). These response rates were achieved despite the fact that the patients had a poor prognosis due to advanced tumor involvement. Kaplan et al reported a 59% response rate, defined as 50% reduction in tumor size, when cisplatin was used as a single agent; a 100% response rate was achieved when combined with doxorubicin in the treatment of salivary gland carcinomas.

The rationale for the 6 cycles of chemotherapy is based on the theoretical principle that at diagnosis a tumor has a population of approximately $10^{12}$ cells. A highly effective (99%) chemotherapy regimen will kill $10^2$ or 2 log-unit cells with each application. Thus, 6 applications ($10^6 \times 10^3 \times 10^5 \times 10^2 \times 10^2 = 10^{12}$) would theoretically be required to effect a "cure." This still leaves $10^3$ to 1 cell. It is presumed the host immune defenses will play a role in eradicating small numbers of cancer cells, such that a cure is possible. This principle is borne out in the demonstrated efficacy of 6 cycles of methotrexate, vincristine sulfate (Oncovin), prednisone, and procarbazine (MOPP) therapy as curative in Hodgkin disease, 6 cycles of cyclophosphamide, methotrexate, and fluorouracil (CMF) in adjuvant breast cancer, or 6 cycles of leucovorin and fluorouracil in adjuvant colon cancer. All these therapies were compared with longer courses of treatment without added benefit. The rationale for continued chemotherapy after surgery is to provide adequate therapy to decrease distant disease relapse using a drug protocol known to work in vivo in the same patient.

Common complications of this chemotherapy program include myelosuppression, nausea, vomiting, fever, sepsis, hair loss, and potential for cardiac damage, renal dysfunction, ototoxicity, and thrombosis or vascular compromise related to the intra-arterial approach. Reported ocular complications due to the regional administration include retinal vascular occlusion, exudative retinal detachment, ophthalmoplegia, optic neuropathy, and maculopathy. In the case of adenocystic carcinoma of the lacrimal gland, in which exenteration is planned, ocular complications to the ipsilateral eye are not a major consideration. Our patients tolerated the administration of chemotherapy well and experienced manageable side effects including hair loss, nausea, and fever. There were no ophthalmic complications to the fellow eye. It must be emphasized that the treatment regimen described is quite toxic, predicted to produce significant, but manageable cytopenia. The risks of neutropenia and sepsis and potential complications from intracarotid catheter placement and chemotherapy infusion including a neurologic catastrophe do exist. This treatment protocol should not be used without adequate support services available.

We believe this is the first report describing the use of neoadjuvant intracarotid chemotherapy in conjunction with the conventional orbital exenteration and radiation for the treatment of locally advanced adenocystic carcinoma of the lacrimal gland. This series also demonstrates for the first time that this combination of drugs and mode of delivery may be effective for this lethal orbital neoplasm. Tumor response is well documented radiographically and histologically in case 1. This patient's 9 1/2-year survival is unprecedented in someone with a nonresectable lesion and a histologic type of adenocystic carcinoma known to confer a poor prognosis. Of the 60 cases reported by Gamel and Font, 54 patients with a basa-roid pattern as a component of the tumor had a 5-year survival rate of 21% and a median survival of 3 years. Patient 2 had a large, long-standing tumor with prominent perineural invasion and bony involvement, features most responsible for early tumor recurrence and ultimate death. Yet despite these poor prognostic indicators, this patient has achieved a survival of 7 1/2 years following this treatment regimen. When compared with the known recurrence rate of nearly 50% by 2 years and a mortality rate of 80% by 10 years, our patients have shown a favorable response. Even though these 2 patients have had prolonged disease-free survival, the possibility of late recurrence does exist. Actuarial analysis performed by Wright et al suggested that the risk of recurrent adenoid cystic carcinoma continues for many years after various modes of therapy. In their series of 38 patients, 1 patient developed recurrence at 7 years and another at 9 years following initial treatment. There were only 2 disease-free survivors after 16 years of follow-up. Clearly, an additional 10 years of follow-up is mandatory for the present cohort to substantiate this form of therapy.

We believe the neoadjuvant chemotherapy strategy used in this treatment protocol, coupled with the selection of an appropriate drug combination, offered the theoretical advantage of “mopping up” occult tumor cells beyond the surgical margins. This approach may prove to be an important difference in minimizing distant disease relapse as compared with conventional therapies. Although the number of patients treated in this series is small, we are encouraged by the early results that intracarotid chemotherapy may be an effective adjunct to the conventional surgical treatment of a devastating disease in which successful therapy has been elusive. As with any new treatment modality of a rare tumor, additional clinical studies, longer follow-ups, and sharing of data are needed to validate efficacy.

Accepted for publication October 27, 1997.

Supported in part by Research to Prevent Blindness, Inc, New York, NY.


Reprints: David T. Tse, MD, Bascom Palmer Eye Institute, PO Box 016880, Miami, FL 33101 (e-mail: dtse@bpei.med.miami.edu).


