Research Article

A Feasibility Study of the Intraductal Administration of Chemotherapy

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Abstract

Preclinical data have shown the potential of the intraductal administration of chemotherapy for breast cancer prevention. Direct translation of this work has been stymied by the anatomical differences between rodents (one duct per teat) and women (5–9 ductal systems per breast). The objective of this phase I study was to show the safety and feasibility of intraductal administration of chemotherapy drugs into multiple ducts within one breast in women awaiting mastectomy for treatment of invasive cancer. Thirty subjects were enrolled in this dose escalation study conducted at a single center in Beijing, China. Under local anesthetic, one of two chemotherapy drugs, carboplatin or pegylated liposomal doxorubicin (PLD), was administered into five to eight ducts at three dose levels. Pharmacokinetic analysis has shown that carboplatin was rapidly absorbed into the bloodstream, whereas PLD, though more erratic, was absorbed after a delay. Pathologic analysis showed marked effects on breast duct epithelium in ducts treated with either drug compared with untreated ducts. The study investigators had no difficulty in identifying or cannulating ducts except in one case with a central cancer with subareolar involvement. This study shows the safety and feasibility of intraductal administration of chemotherapy into multiple ducts for the purpose of breast cancer prevention. This is an important step toward implementation of this strategy as a “chemical mastectomy”, where the potential for carcinogenesis in the ductal epithelium is eliminated pharmacologically, locally, and without the need for surgery. *Cancer Prev Res*: 6(1); 51–58. ©2012 AACR.

Introduction

Everyday, approximately 110 women die from breast cancer, and nearly 800 new cases of invasive or *in situ* breast cancer are diagnosed (1). The vast majority of breast cancers begin locally, in the epithelial lining of just one of the 5 to 9 ductal lobular units in the breast. Precancerous lesions in the duct, such as atypical ductal hyperplasia (ADH), are thought to progress to ductal carcinoma *in situ* (DCIS) and then to invasive cancer (2–5). Currently available breast cancer prevention strategies include surgical options such as oophorectomy (removal of the ovaries) and/or bilateral mastectomy, or pharmaceutical therapy such as tamoxifen (6–13). Other drugs such as aromatase inhibitors and other selective estrogen receptor modulators (SERM) have been studied as preventative agents, but clinical uptake has been limited. In addition, none of the options for prevention are without side effects or consequences (9–14). Thus, current prevention options exhibit a range of physical and emotional effects (15), all in an effort to prevent a local condition. Contrary to some malignancies, few attempts have been made in breast cancer to exploit the locality of the disease. Local therapy, which offers the potential of providing prolonged drug concentrations at the site of disease and minimizing systemic exposure to toxic chemotherapeutic agents, has found success in other cancers, including intravesical treatment of bladder cancer and intraperitoneal treatment of ovarian cancer (16, 17). In breast cancer, local therapy could enable both anatomic and molecular-targeted therapy, possibly eliminating the need for surgery altogether by providing a pharmacologic method for eradicating premalignant tissue in the breast. This “chemical mastectomy” could be used as a strategy for breast cancer prevention. Unfortunately, our lack of understanding of ductal anatomy and the dearth of methods to access the ducts has hindered the development of intraductal therapy for breast cancer. The description of the number of ducts found per breast depends on the technique of study (18). Researchers who have cannulated the ductal orifices in the nipple in vivo, all confirm 5 to 9 ductal systems (19–22), whereas those who have transected the nipple in mastectomy specimens...
have documented 22 to 25 tubular structures (21, 23–25). Despite this discrepancy, Love and colleagues have shown that cannulation of all the orifices on the nipple surface is sufficient to fill all the ductal systems and that fluid instilled into the ducts reaches the terminal duct lobular units (TDLUs; ref. 19). In 2004, Coullet and colleagues confirmed this in a pilot study in which 3 to 5 mL of nanoparticles containing 6% epirubicin was administered into tissue specimens postmastectomy and assessed pathologically, showing that intact epirubicin was seen in the terminal lobules in 62% of specimens (26). Together, these studies have shown that fluid instilled into the breast ducts through the orifices on the nipple can access all the ductal units and reach the TDLUs, supporting this strategy for administration of anticancer agents.

Preclinical data have shown that intraductal therapy, in which chemotherapy or another anticancer agent is delivered directly into a duct through the nipple, prevents the development of breast cancer. For example, Okugawa and colleagues showed that rats with development of breast cancer. For example, Okugawa and colleagues showed that rats with N-methyl N-nitrosourea (MNU)-induced breast tumors exhibited significant reduction in tumor burden and total number of mammary carcinomas when treated with intraductal paclitaxel (27). Similarly, Sukumar and colleagues have shown that intraductal administration of various anticancer drugs, such as pegylated liposomal doxorubicin (PLD), 4-hydroxytamoxifen carboplatin, methotrexate, nanoparticle albumin-bound paclitaxel, and 5-fluorouracil was associated with a significant reduction in tumor formation or protected against tumor development in the MNU model, and also minimized the toxic effects of the drugs (28, 29). The same group has also shown that in the HER2/neu transgenic mouse (neu-N) model, which spontaneously develops neu-overexpressing multifocal mammary adenocarcinoma beginning at approximately 4 to 5 months of age, intraductal PLD treatment resulted in significantly reduced risk of developing breast tumors.

The translation of intraductal therapy from animal models to the clinic holds the potential for breast cancer prevention without surgery or systemic drug treatment. Despite the success of preclinical studies, it is important to note the unique challenges in moving from rodents to humans. In contrast to humans, who have 5 to 9 ductal systems that converge in a single nipple, rodents have 10 to 12 mammary glands, and each gland has its own teat. These anatomical distinctions underscore the importance of testing the safety and feasibility of intraductal therapy in humans. To that end, Stearns and colleagues recently conducted a clinical trial in which 17 women scheduled for mastectomy for invasive carcinoma were trained by the principal investigator to conduct the procedure under local anesthesia and spend 3 to 7 days as in-patients awaiting surgery. This monitored sojourn gave us the opportunity to conduct the procedure under local anesthesia and spend several days observing any local or systemic complications before mastectomy.

Materials and Methods

Study location
We elected to conduct this study in Beijing, China because the logistics of breast cancer care were more conducive to several days of in-hospital clinical monitoring after treatment and before definitive surgery. Unlike treatment in the United States, women were admitted from the clinic after diagnosis and spent 3 to 7 days as in-patients awaiting surgery. This monitored sojourn gave us the opportunity to conduct the procedure under local anesthesia and spend several days observing any local or systemic complications before mastectomy.

Subjects
The study underwent thorough review by a U.S. Institutional Review Board (IRB) as well as the IRB of the Cancer Hospital, Chinese Academy of Medical Sciences (Beijing, China). Women were recruited for the study if they were patients who had been diagnosed with breast cancer. The consent form was reviewed in Chinese by their local physician. The study was conducted and monitored with assistance from a Chinese contract research organization (CRO, Excel PharmaStudies). The local surgeons were successfully trained by the principal investigator to conduct the procedure of duct cannulation on postmastectomy breasts over one afternoon.

A total of 31 subjects scheduled to undergo mastectomy for breast carcinoma participated in this study between March 2007 and January 2008. One patient with a central lesion that precluded duct cannulation was withdrawn. Of the 30 remaining subjects, 15 were in the carboplatin arm and 15 were in the PLD arm, and each arm was divided into
3 dosage groups with 5 subjects per group (Table 1). In the carboplatin arm, the dosage groups were 60, 120, and 300 mg/breast, whereas in the PLD arm, the dosage groups were 10, 20, and 50 mg/breast.

**Intraductal administration of carboplatin and PLD**

The study drug was administered once into 5 to 8 ducts by intraductal instillation up to 7 days before mastectomy. The procedure was conducted, using aseptic technique, under local anesthesia in a treatment room on the surgical floor. After prepping, lidocaine without epinephrine was injected directly into the nipple. This not only established anesthesia but also highlighted the duct orifices as dimples on the distended nipple surface. The duct orifices were identified with an ultrathin dilator (Cytyc) and then cannulated with a single lumen sialogram catheter. Once all the obvious ducts had been cannulated, the total assigned dose of the drug per breast was divided by the number of ducts to be treated and, between 0.5 and 6 mL, was instilled into each duct. In the carboplatin arm, 5 subjects received a total (per breast) of 60 mg of drug, 5 subjects received 120 mg, and 5 subjects received 300 mg. In each case, the drug was delivered as a 10 mg/mL solution. In the PLD arm, 5 subjects received a total of 10 mg of drug, 5 subjects received 20 mg, and 5 subjects received 50 mg. In each case, the drug was delivered as a 2 mg/mL solution. At the end of the procedure, the catheter was replaced by a knotted prolene marker in each treated duct and covered with a sterile plastic dressing (Tegaderm) that remained until after the planned mastectomy. The total procedure took as little as 30 minutes and not longer than 90 minutes.

**Pharmacokinetic analysis**

After intraductal carboplatin administration, venous blood samples were taken at 15 and 30 minutes, 1.5, 4.5, 16, 24, 48, and 72 hours, and then daily until mastectomy and 24 hours after mastectomy. After intraductal PLD administration, venous blood samples were taken at 30 minutes, 1, 4, 12, 24, 48, and 72 hours, and then daily until mastectomy and 24 hours after mastectomy. Human plasma samples were analyzed at the Chinese Center For Disease Control And Prevention, National Institute of Occupational Health and Poison Control (Beijing, China). Samples were analyzed to determine drug concentration levels in the plasma of each subject. For carboplatin, the assay was developed and validated in human plasma ultrafiltrate that was obtained from stored frozen plasma using flameless atomic absorption spectrometry for the detection of platinum. Total plasma doxorubicin was assayed by high-performance liquid chromatography-mass spectrometry (HPLC/MS).

**Pathologic examination**

The planned mastectomy was conducted 2 to 7 days after drug administration. After the breast was removed, the specimen was taken to pathology where the Tegaderm was removed, the markers were extracted, and a 0.1% methylene-blue gelatin dye was instilled into each treated duct before fixation to allow for identification on pathology. The entire breast was then immersed in a large container containing 10% formalin overnight. After adequate fixation, the specimen was sliced at 1-cm interval horizontally. A digital photo was taken for each slice of the breast. For each mastectomy specimen, in addition to routine sections of nipple, areola area, tumor, and margins, additional multiple sections were taken including a whole-face cross section of the nipple, 1 to 2 whole-face cross sections of the areola ring, representative sections of tumor (with or without dye), dye-stained nontumor areas (containing cannulated ducts), and nondye-stained nontumor random areas (containing noncannulated ducts). Typically for each patient sample, between 15 and 30 sections were examined.

Tissue sections were processed overnight. Microscopic sections 3 to 5 μm thick were cut and stained with hematoxylin and eosin. The sections were reviewed by 2 pathologists (X. Yang and J. Rao) without specific knowledge of dose levels of each drug treatment arm. Because this was a feasibility study, our analysis was limited to comparison between untreated and treated ducts; the study was not designed to assess pathologic changes within a duct before and after treatment. Inflammatory response was graded as no change, mild, moderate, or severe change; where no change represented no discernible inflammatory cell infiltration in the section; mild change

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<th>Study arm</th>
<th>Dose per duct (mg)</th>
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<td>Group</td>
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<td>Carboplatin 10 mg/mL</td>
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was represented by scattered inflammatory infiltration only seen on high magnification (100×); moderate change signified inflammatory infiltration at moderate magnification (400×); and severe change was marked by inflammatory infiltration seen on low magnification (40×). The type of inflammatory infiltration was also characterized as acute, chronic, or mixed and recorded as such. Ductal epithelial cell changes were graded as no change, mild, moderate, or severe change, where no change correlated to no discernible ductal epithelial cell change including loss of epithelial cells; mild change indicated less than one-third epithelial cell loss, with remaining epithelial cells showing slightly more eosinophilic cytoplasm, slightly enlarged nuclei with smudged chromatin, and inconspicuous nucleoli only seen on high power (400×); moderate change indicated about one- to two-thirds epithelial cell loss, with remaining epithelial cells showing eosinophilic cytoplasm, enlarged nuclei with smudged chromatin, and small but centrally located single nucleoli seen on moderate power (100×); and severe change indicated more than two-thirds epithelial cell loss, with remaining epithelial cells showing abundant eosinophilic cytoplasm, enlarged nuclei with smudged chromatin, and prominent but centrally located single nucleoli seen on low power (40×).

Results

Intraductal administration of chemotherapy

Intraductal therapy was conducted on a total of 30 subjects ranging in age from 25.9 to 75.6 years, with a mean age of 50.8 years in the carboplatin arm and 55.0 years in the PLD arm. Twenty of 30 subjects were postmenopausal; of these, 11 were in the carboplatin arm and 9 were in the PLD arm. There were no pretreatment vital signs, physical exam findings, or medical events that disqualified a patient from the study. Intraductal administration of chemotherapy was shown to be feasible under local anesthesia in a treatment room; the investigators had no difficulty identifying or cannulating 5 to 8 ducts (Fig. 1A–C) except in one case with a central cancer with subareolar involvement. Intraductal administration of chemotherapeutic agents was generally well tolerated. The only concerns identified with the cannulation of the ducts and infusion of the drugs was mild discomfort, which appeared to be associated with the rate as well as volume of infusion and minimal fluid leakage from around the duct.

In the carboplatin arm (Table 1), no subjects experienced breast redness or swelling at the lower doses, whereas 3 subjects (60%) experienced mild erythema and swelling following the procedure at the highest dose. Four (80%) of the women who received the highest dose of carboplatin experienced mild nausea and vomiting, suggesting systemic exposure. In the PLD arm (Table 1), most women had mild erythema and swelling over 72 hours following drug administration. The women receiving the highest dose of PLD experienced nontender local erythema of the breast limited to the area covered with Tegaderm, which persisted until the time of surgery (Fig. 1D). This skin reaction is consistent with reported PLD skin toxicities (35, 36). None of the adverse events associated with treatment of either drug were considered serious.

Clinically significant laboratory adverse events were limited to decreases in hemoglobin following mastectomy, consistent with blood loss. Neither leucopenia nor thrombocytopenia was observed in the study. There were no relevant changes in blood pressure, respiratory rate, or body temperature attributed to treatment with either drug when administered intraductally.

Pharmacokinetic analysis

Pharmacokinetic evaluation showed that there were detectable levels of both drugs in the systemic circulation. For carboplatin, the pharmacokinetic analysis was designed to assess the disposition of carboplatin after intraductal administration. Following the first intraductal administration, mean plasma concentration–time profiles had an early peak of 30 minutes followed by a clearance with an average half-life of 2 hours and 20 minutes for all doses. Mean plasma area under the curve (AUC0–∞) estimates...
increased in an apparently linear manner with dose (Fig. 2). The observed systemic exposure based on the carboplatin ultrafiltrate plasma profile was highly correlated with systemic exposure expected from a carboplatin intravenous administration, suggesting that the subject would have essentially the same systemic exposure from either route of administration.

Systemic doxorubicin exposure was erratic both within and between women in each dosing group. AUC was poorly characterized from the time points collected; therefore, an estimate of bioavailability after intraductal administration could not be made with any confidence. In general, however, doxorubicin was slowly absorbed into the systemic circulation. Peak plasma concentrations were linear with dose and approximately 1 of 5 of what would be expected from the equivalent intravenous dose, although no doxorubicin dose proportionality was observed. There was no detectable doxorubicin metabolite in the blood, and no systemic toxicity was observed. The local erythema effect was likely from stromal rather than capillary trapping of liposomes.

Pathologic effects of intraductal chemotherapy

Though the time between intraductal therapy and mastectomy was short (2–7 days), distinct dose-related effects were observed in the treated ducts. We provide here a relatively qualitative assessment of these effects, as a more quantitative analysis will be published elsewhere.

Pathologic examination was used to objectively assess the local effects of carboplatin and PLD on nipple skin, benign and malignant ductal cells, and the surrounding fibroadipose tissues. Specifically, the effect of the drugs on cell death (apoptosis and necrosis), proliferation (mitosis), and inflammatory reaction were examined. During our initial data analysis, we found that many of the sections from tumor areas did not contain ducts and dye. This was not unexpected as no effort was made to cannulate the duct involved with cancer. As our goal was to compare...
Inflammatory responses and epithelial cell changes in ducts with dye and without dye, not to study the effect of each drug on cancer cells per se, data from tumor sections without ducts and dye were not further analyzed. However, when ducts were seen in the random sections (collected from nontumor- and non-dye-stained areas), they consistently showed no epithelial changes and served as a background for the subsequent analysis. In ducts that received dye, the dye was observed in areas of DCIS and invasive carcinoma as well as in TDLUs (Fig. 3A and B), suggesting that the drugs were widely distributed throughout the ductal systems.

With carboplatin, there was a dose-dependent mild to moderate inflammatory response as well as a dose-dependent increase in ductal epithelial degeneration (Fig. 3B). There were no substantial dose-related changes in inflammation (either degree or type) of the nipple or areola ring. In the dye-stained areas, no severe inflammatory response was observed, but there were dose-dependent changes in the intensity of inflammation in the ducts, with an increase of mild and moderate inflammation noted with an increase in dose levels. The type of inflammation was either mixed or chronic. This relationship was observed in both ducts and surrounding fibroadipose tissue. In ductal epithelial cells, initial evaluation found that in sections from nipple and areola ring, there were consistent, severe losses of ductal epithelial cells in all dye-stained ducts, whereas there were none in ducts without dye regardless of dose levels. As we could not determine whether such loss of epithelial cells was due to drug effect or mechanically induced by ductal cannulation, the epithelial cell changes in nipple and areola ducts were not analyzed further. There were more epithelial cell changes of any degree in the high-dose group versus the low- and middle-dose groups, even in the ducts without dye. However, there were significantly more epithelial cell changes in the ducts with dye than the ducts without dye at all dose levels. In addition, while there were mostly mild epithelial cell changes seen in ducts with dye, the ducts with dye showed more changes than those without dye. Furthermore, there was a dose–response relationship observed between dosage levels and epithelial cell changes.

With PLD, there was a trend of dose-related increase in degree of inflammation, with low dose showing a few cells with mild inflammation, mid-dose showing moderate inflammation, and high dose showing severe inflammation, but the difference did not reach statistical significance probably due to the small sample size ($P = 0.18$; data not shown). No severe inflammatory changes were observed in any dose group. In the epithelial cell analysis, sections from nipple and areola ring showed consistent severe losses of ductal epithelial cells in all the dye-stained ducts, whereas there were none in ducts without dye regardless of dose levels. As with carboplatin, because we could not determine whether such loss of epithelial cells was due to drug effect or mechanically induced by ductal cannulation, the epithelial cell changes in nipple and areola ducts were not analyzed further. There was an increase of epithelial response to the PLD treatment in ducts with dye versus ducts without dye in all dose levels (Fig. 3C). While no significant dose–response relationship was observed with epithelial changes, the 10 mg group seemed to have more of a mild to moderate degree of change; the 50 mg group showed more severe epithelial changes; and no changes were observed in ducts without dye.

Discussion
This study shows that intraductal therapy with carboplatin or PLD can be safely administered with an acceptable local side effect profile in patients undergoing mastectomy within 1 week of drug administration. For carboplatin, there was a dose–response increase in the mild...
to moderate inflammatory response, as well as a dose-response increase in the duc tal epithelial cell changes suggestive of cellular degeneration. For PLD, there was a trend of increased mild to moderate inflammatory response in the nipple, dye-stained ducts, and stromal tissue, and there was a significant increase of epithelial response to the PLD treatment in ducts with dye versus ducts without dye at all dose levels. Notably, our results show that chemotherapy agents can be administered to multiple ducts within a single breast with no apparent harm to tissue outside the ducts. Though future studies are needed to more fully characterize the pharmacokinetics, long-term safety, and efficacy of intraductally administered drugs, the feasibility, relative safety, pharmacokinetic properties, and pathologic effects observed in this study support the exciting prospect of an intraductal approach for breast cancer prevention.

An important advance achieved in this study is the demonstration of the relative ease with which multiple ducts in patients with invasive cancer can be cannulated. This supports the implementation of this method as a chemopreventive strategy for high-risk women and those with DCIS and ADH. In these cases, stripping of the epithelium lining that results from intraductal administration of appropriate anticancer agents would eliminate the potential for transformation of duc tal epithelial cells to their cancerous counterparts. In women with DCIS or atypical hyperplasia, the affected duct could be treated, leaving the healthy ducts intact, and we have preliminary evidence of the feasibility of this strategy (manuscript in preparation). However, in high-risk women, because it is not known a priori which duct will become cancerous, treatment of all the ducts may be the most effective approach.

Our pharmacokinetic and pathologic analysis uncovers important characteristics of the drugs examined in this study that will inform drug selection for future studies. After intraductal administration, both carboplatin and PLD were distributed throughout the duc tal systems and caused degenerative effects on the epithelial lining the ducts. However, carboplatin rapidly appeared in the bloodstream, which would lead to adverse systemic side effects associated with systemic delivery of this agent. The pharmacokinetic properties of the drug likely contributed to its ability to quickly escape the ductal systems, negating many of the benefits that intraductal therapy was designed to fulfill. This suggests that drugs formulated to prolong stability and decrease permeability, such as PLD, might be more efficacious as intraductal therapy agents. Indeed, systemic exposure of PLD was much reduced from that expected from a similar intravenous dose. To this point, in a recent study examining the retention of fluorescein-labeled PEG nanocarriers in rat mammary ducts, it was concluded that the ducts were highly permeable and that both size and shape of the nanocarriers influenced nanocarrier retention, offering insight into the future design of intraductal drug delivery agents (37).

The basis for the erratic pharmacokinetic profile of PLD is unclear. The liposomal formulation and delayed appearance in the blood suggest that the drug may be better retained in the duc tal systems than carboplatin. However, it is possible that either during the drug instillation process or as a result of the tumor, the integrity of some of the ducts in any given subject was damaged. In healthy women, ductal lavage, a procedure in which fluid is instilled into and then retrieved from the duct under ultrasound monitoring to sample ductal fluid, results in a perforation rate of 7% to 10% (38). In women with DCIS, the perforation rate is somewhat higher at approximately 25% (unpublished observations), possibly due to disruption of basement membrane integrity from the DCIS or the increased pressure in the duct due to pathology. In this study on women with invasive cancer, it is possible that the ducts affected by the cancer were compromised, and PLD instilled into those ducts might have escaped to bloodstream. This could account at least, in part, for the inconsistent pharmacokinetic behavior observed. In the clinical trial conducted by Stearns and colleagues, ductograms were conducted before intraductal drug administration to assess the integrity of the ducts. If the ducts were perforated, the subject was excluded from treatment. In their pharmacokinetic analysis, significantly less, and often no doxorubicin, or its metabolite doxorubicinol, were detected in the plasma of women receiving intraductal PLD compared with the micromolar levels observed in subjects receiving intravenous PLD. This supports our hypothesis that duct perforation may be responsible for the erratic PLD pharmacokinetics observed in our study. The pathologic and pharmacokinetic analysis of both carboplatin and PLD suggest that while these drugs were a reasonable starting point, other anticancer agents and/or formulations should also be explored for intraductal therapy. Recent preclinical studies in rats examined intraductal treatment with either cytotoxic agents such as carboplatin, nanoparticle albumin-bound paclitaxel or PLD, or DNA-damaging antimetabolites such as 5-fluorouracil or methotrexate (29). While all drugs tested exhibited some protection from tumor growth, PLD-treated ducts also exhibited a loss of density of ductal outgrowth, and 5-fluorouracil was associated with the greatest antitumor effect. The distinct effects of the drugs in these preclinical studies, coupled with our findings of the pharmacokinetic and pathologic behavior of carboplatin and PLD in women, warrants exploration of additional anticancer agents and drug formulations for intraductal therapy.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.Y. Rao, H. Yang, B. Zhang

Writing, review, and/or revision of the manuscript: S.M. Love, E.J. Gordon, J.Y. Rao, G. Chen

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Acknowledgments

The authors thank Sarawati Sukumar, Troy Brenner, Meghan Brennan, and Gabriella Poitier for their help in the design and management of the study.

References


Correction: A Feasibility Study of the Intraductal Administration of Chemotherapy

In this article (Cancer Prev Res 2013;6:51–58), which was published in the January 2013 issue of Cancer Prevention Research (1), the publisher failed to identify Baoning Zhang as co-corresponding author. Dr. Zhang’s contact info is as follows: Baoning Zhang, Department of Abdominal Surgery, Cancer Institute/Hospital, Chinese Academy of Medical Sciences, No. 17 Panjiayuannanli, Chaoyang District, P.O. Box 2258, Beijing 100021, P.R. China. E-mail: CBD@cicams.ac.cn. The publisher regrets the error.

Reference


Published OnlineFirst April 10, 2013.
doi: 10.1158/1940-6207.CAPR-13-0082
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