Radiation and Intra-arterial Cisplatin Effects on Arteries and Free Tissue Transfer

Joseph Valentino, MD; Lisa Weinstein, MD; Richard Rosenblum, MD; William Regine, MD; Michael Weinstein, MD

Objectives: To determine the histopathologic effect of combined intra-arterial cisplatin administration and hyperfractionated external beam radiation treatment (HYPERRADPLAT) on potential recipient arteries in the neck and to analyze the efficacy of free tissue transfer (FTT) in patients undergoing HYPERRADPLAT.

Design: Cisplatin-perfused and nonperfused artery segments were harvested during planned interval neck dissection performed 6 to 10 weeks after HYPERRADPLAT. These segments were evaluated by light microscopy and transmission electron microscopy. All patients undergoing FTT after HYPERRADPLAT were reviewed retrospectively.

Setting: Academic medical center.

Patients and Intervention: Eight patients undergoing HYPERRADPLAT for head and neck squamous cell carcinoma and planned interval neck dissection were prospectively studied. All patients had a perfused artery sampled, and 3 also had a nonperfused (control) artery sampled. Five patients undergoing FTT after HYPERRADPLAT were retrospectively analyzed for outcome of FTT.

Results: No consistent histological or ultrastructural differences were detected between injected and noninjected arteries. Both demonstrated intimal thickening, collagen and elastin deposition in the intimal layer, and, occasionally, intimal smooth muscle proliferation. A smaller fraction of the injected and noninjected arteries demonstrated smooth muscle cell vacuolation, elastic fiber degeneration, and calcific deposits. Four of 5 FTTs in patients undergoing HYPERRADPLAT were successful.

Conclusions: The changes seen in the injected and noninjected arteries were characteristic of ionizing radiation. Arteries treated with HYPERRADPLAT had no observable difference from vessels treated with radiation alone. These vessels can be used with caution as recipient vessels for FTT. Further clinical experience is needed to establish the expected results of FTT using these arteries.


HERAPY FOR head and neck cancer has evolved to include more intensified therapy to attain greater rates of organ preservation. We have increased the dose of radiation therapy, and in many cases reirradiated tissues, to far beyond what was previously thought to be the “limits of tissue tolerance.” In addition, we have added chemotherapy sensitization to radiation, improving control of cancer. Tissue manifestations of toxic reactions to that therapy and surgical salvage of treatment failures place greater demands on the reconstruction. Many centers, including the University of Kentucky Chandler Medical Center, Lexington, are using intra-arterial chemotherapy concurrently with radiation therapy to treat head and neck cancer with good results. We have not eliminated the need for surgery and surgical reconstruction in these patients. Bringing healthy, unirradiated tissue into these wounds is critical for optimizing healing, and free tissue transfers (FTTs) frequently provide the best tissue for these wounds. Most surgeons believe that a history of irradiation makes FTT more difficult, and these newer, intensified locoregional treatment regimens might make it even more difficult. To our knowledge, the world’s literature does not describe the changes to treated vessels and the impact on FTT success of this treatment.

The earliest experiences of FTT in head and neck reconstruction warned of anastomosis failure, especially in the previously irradiated patient. Concerns regarding the vessel anastomoses’ success spawned a variety of studies examining the effect of various factors, including stud-
PATIENTS AND METHODS

PATIENTS

Forty patients at the University of Kentucky Chandler Medical Center and Lexington Veterans Affairs Medical Center underwent hyperfractionated external beam radiation treatment (HYPER-RAD-PLAT) and intra-arterial cisplatin administration for stage III and IV head and neck squamous cell carcinoma. Six of these patients underwent attempted microvascular reconstruction of the head and neck area as part of their treatment. Their medical charts were reviewed and summarized. Another 8 patients underwent surgical resection after completion of irradiation and chemotherapy. At the time of surgery, an injected artery was identified and harvested for analysis. In 3 of these 8 patients, a noninjected artery was harvested to serve as a control to analyze for the differential effects of chemotherapy perfusion. No arteries were harvested that would not normally be taken as part of the surgery to avoid adding morbidity to the operation. Seven of these patients were undergoing planned interval radical neck dissections for N2a or N3 neck disease. The eighth patient had a pharyngeal resection for persistent microscopic disease within a large radiation ulcer. He had a massive T3 N0 M0 squamous cell carcinoma lesion of the posterior oropharynx that had a complete clinical response; however, persistent microscopic disease was discovered on a biopsy sample taken 8 weeks after therapy.

PROCEDURES

Operations were performed 6 to 10 weeks after completion of irradiation and chemotherapy. Segments of artery, 3 to 5 mm long, were harvested and immediately placed on saline solution–moistened gauze for transport to the surgical pathology suite. None injected arteries from the same surgical field were harvested and transported in the same fashion. Artery segments were serially sectioned, and 1-mm cross sections were fixed in 3% glutaraldehyde and 0.2 mol/L cacodylate buffer (pH 7.3-7.4) for at least 3 hours at 5°C. After glutaraldehyde fixation, artery segments were postfixed in osmium tetroxide, infiltrated with propylene oxide, and embedded in epon araldite embedding medium. Sixty-nanometer sections were made with a diamond knife and examined with a transmission electron microscope (model CM-100; Philips, Eindhoven, the Netherlands). Representative areas of the arteries were photographed and reviewed by a pathologist (L.W.).

Intervening cross sections of artery were fixed in 10% neutral buffered formalin and processed for routine hematoxylin-eosin staining. The pathologist examined hematoxylin-eosin–stained sections under light microscopy. Transmission electron microscopic and light microscopic findings were recorded for each injected and noninjected artery. Features assessed included evidence of endothelial cell damage (cytoplasmic inclusions and fibrin and platelet deposits), evidence of damage to the tunica intima (thickening, elastin and collagen deposition, smooth muscle proliferation, and intimal loss), disruption of the internal elastic lamina, and damage to the tunica media (smooth muscle cell vacuolation, elastic fiber degeneration, and calcific deposits).

This study was reviewed and approved by the University of Kentucky Internal Review Board.

CLINICAL OUTCOME OF FTT

One of 6 patients treated was a surgical failure who had disease infiltrating his radial forearm free flap. This artery was perfused with cisplatin during HYPER-RAD-PLAT without consequence to the flap’s viability. Five of 6 patients underwent FTT procedures 6 to 10 weeks after completion of HYPER-RAD-PLAT. Three patients had residual gross disease at the primary site requiring FTT reconstruction; they had oropharyngeal defects and underwent reconstruction using a rectus abdominus flap (n = 2) or a latissimus dorsi flap (n = 1). Another patient had a nonhealing ulcer with suspicious pathological findings on biopsy examination and no disease in the resected specimen. His hypopharyngeal de-
fect was repaired with a radial forearm flap. The fifth patient had a pathologic fracture from a tumor on the floor of the mouth that occurred during radiation therapy. He required a free fibula reconstruction. All patients were treated with dextran 1 followed by dextran 40 continuous infusion at 25 mL/h. Vessels were routinely irrigated with heparin sodium solution. The latissimus dorsi flap was unable to be transferred in one patient because of the inability to establish arterial inflow. This patient experienced a cerebrovascular accident secondary to thrombosis of the internal carotid artery and on subsequent workup was found to have a hypercoagulation disorder. The 4 other patients had successful FTTs. In one patient, the initial release of the clamps from the artery resulted in no flow and the anastomosis was cut down and redone. A single bolus of heparin was given, and the flap survived without incident.

**PATHOLOGICAL ANALYSIS OF ARTERIES**

All 11 arterial specimens—8 perfused and 3 control—were analyzed. Nearly all of the arteries examined (10 of 11) showed evidence of chronic intimal damage, including intimal thickening and intimal collagen and elastin deposition (Figure 1). Fewer arteries (5 of 11) showed intimal smooth muscle proliferation, and these were roughly proportional between injected and noninjected arteries (Figure 2). A small proportion of injected and noninjected arteries showed evidence of chronic damage to the tunica media, including smooth muscle cell vacuolation (Figure 3, left), calcific deposits (Figure 3, right), and elastic fiber degeneration (Figure 4) (4 of 11 for each). Light microscopy and transmission electron microscopy demonstrated the least evidence of acute damage to the tunica intima in injected and noninjected arteries. Only 4 of 11 arteries showed lipidlike deposits in endothelial cells (Figure 5, right), and only 3 of 11 arteries showed disruption of the internal elastic lamina. Two of these were caused by the presence of large calcific deposits in the tunica media. Finally, no arteries demonstrated fibrin or platelet thrombus formation or denudation of the tunica intima.

**COMMENT**

Capillaries seem to be more susceptible to the effects of radiation than do larger vessels. Those ranging from 0.8 to 1.5 mm in diameter, used in microvascular anasto-
mosis, are moderately radiosensitive.10,14 Actively dividing cells such as vascular endothelium are the most sensitive to ionizing radiation; however, all layers of the vessel wall are affected.14,15 The changes that we have seen in these intensely treated vessels have all been reported in irradiated vessels.3,10 Use of HYPERPLAT does not seem to produce new, unreported histopathologic features in the 1- to 2-mm arteries that we sampled.

Our data support the supposition that any intimal injury caused by the chemotherapy perfusion is histopathologically undetectable 7 to 10 weeks after treatment. Furthermore, the cisplatin-perfused vessels are not substantially different from the nonperfused vessels.3,10 Use of HYPERPLAT does not seem to produce new, unreported histopathologic features in the 1- to 2-mm arteries that we sampled.

Figure 3. Left, Cisplatin-injected artery with arrow indicating smooth muscle cell vacuolation (hematoxylin-eosin, ×100). Right, Cisplatin-injected artery with arrowheads indicating medial calcification disrupting internal elastic lamina (toluidine blue, ×50).

Figure 4. Cisplatin-injected artery with arrowhead indicating medial elastic fiber degeneration (toluidine blue, ×100).

The surgeon must consider the possible implications of these changes when performing microvascular surgery. The intima is frequently hypertrophied and nodular. Furthermore, the transmission electron microscopic findings show frequent irregularities within those endothelial cells that reflect injury, but the implication on their ability to repair or survive the injury of clamping, suturing, and other such manipulation is unknown. De Wilde et al16 showed much higher rates of intramural thrombus formation and platelet aggregation to the endothelium near and at the anastomosis site far more commonly in the irradiated than the nonirradiated vessels. The observed damaged endothelium in these human vessels might be at risk for this type of formation as well. Although there is no clear evidence that anticoagulative therapy is needed in routine FTT, this group of patients might benefit. The fragility of these treated, irradiated vessels might warrant more liberal use of anticoagulant agents locally and systemically to avoid inflow problems. Because our data are from a small group of patients, definitive recommendations cannot be made.

The damage to irradiated vessels is transmural, and this is also seen in our patients. The calcifications that are occasionally substantial enough to disrupt the internal elastic lamina might render the intima more readily separated from the media during surgical manipulation. This manipulation is more intense in these heavily treated tissues to simply expose these vessels. The adventitial fibrosis and inflammation also increases the amount of manipulation needed to prepare the vessels for anastomosis. The reconstructive surgeon should anticipate increased time in dissecting out and preparing recipient vessels and might want to do this himself or herself rather than relegating the task to another surgeon. Furthermore, during the anastomosis procedure the vessel must be handled with increased attentiveness to basic principles. Even simple events such as turning a paired or framed vascular clamp over must be done with great caution. We frequently avoided their use altogether if the vascular stump of the donor vessel was short. The use of vessel dilators might easily disrupt the intima or tear a disrupted internal elastic lamina. More cautious inspection of the intima is warranted because it might be easily torn or separated from the media.
More study of the damage to human vessels during the various forms of combined therapy is needed. Many microvascular surgeons believe that vessels undergoing combined therapy are more fragile to work with, and this is well studied. Defining the exact incidence of these injuries would be helpful to the reconstructive surgeon in choosing optimal vessels. The study of FTT outcome in patients treated with multimodality organ preservation therapies might not show the same degree of success that we have come to expect in patients treated with radiation alone. Furthermore, HYPERRADPLAT might produce different arterial damage than standard fraction radiotherapy. Correlative studies of reconstruction outcome and the histopathologic features of the recipient vessels will require involvement by multiple institutions because so few of these patients undergo resection of the primary tumor.

CONCLUSIONS

The injury to medium arteries treated with HYPERRADPLAT and directly perfused with high-dose cisplatin is similar to that of nonperfused arteries.

The light microscopic and transmission electron microscopic findings of these arteries are similar to those already reported in irradiated vessels.

Early clinical experience with microvascular surgery in these patients shows no contraindication to the use of these vessels; however, caution in the handling of these arteries should be exercised until large clinical series of flaps show equivalent patency rates to those of non-irradiated arteries.

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Reprints: Joseph Valentino, MD, Division of Otolaryngology–Head and Neck Surgery, University of Kentucky Chandler Medical Center, 800 Rose St, Room C236, Lexington, KY 40536-0084 (e-mail: jvale00@pop.uky.edu).

REFERENCES