Intraoperative High-Dose Rate of Radioactive Phosphorus 32 Brachytherapy for Diffuse Recalcitrant Conjunctival Neoplasms
A Retrospective Case Series and Report of Toxicity

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IMPORTANCE Adjunct treatments for conjunctival malignancies are needed when standard therapy provides limited benefits or fails.

OBJECTIVE To describe the results of patients with diffuse conjunctival neoplasms treated with radioactive phosphorus 32 (32P)-impregnated flexible film.

DESIGN, SETTING, AND PARTICIPANTS This retrospective case series between January 1, 2010, and January 1, 2013, was conducted at Memorial Sloan-Kettering Cancer Center, a tertiary referral center. The study was conducted on 7 eyes of 6 patients treated for diffuse conjunctival squamous cell carcinoma, sebaceous carcinoma, or lymphoma that had recurrent or residual disease after primary treatment.

INTERVENTIONS Patients underwent mapping biopsies and detailed conjunctival drawings to delineate the pathologic extent of the disease. The brachytherapy film used for treatment was the RIC Conformal Source Model 100 (RIC-100, RI Consultants). The RIC-100 is a flexible, thin (approximately 0.5-mm) film made of a polymer chemically bound to 32P. The radioactive 32P film was placed intraoperatively, allowed to stay in place until the prescription dose was reached, and then removed. The median dose at the prescription point (1 mm from the surface of the film) was 15 Gy (range, 5-17 Gy).

MAIN OUTCOMES AND MEASURES Patients were tested for best-corrected visual acuity, recurrence-free survival, and adverse events scored by using the Adult Comorbidity Evaluation–27 scale.

RESULTS Between 2010 and 2013, 7 eyes of 6 patients were treated. The median age of patients was 70 years. All patients had a recurrent or persistent neoplasm. Four patients with squamous cell carcinoma, 1 with sebaceous carcinoma, and 1 with metaphonous bilateral lymphomas were treated. The median treatment time was 19 minutes (range, 10-52 minutes). The median follow-up was 24.9 months (range, 3.1-38.2 months). Recurrence-free survival 24 months after brachytherapy was 75% (95% CI, 19-89.1). Two moderate adverse events and 1 severe adverse event occurred. Visual acuity was stable or improved in 5 of the 7 eyes (ie, better than 20/70 in the 5 patients who retained their treated eye).

CONCLUSIONS AND RELEVANCE Our results show the use of an intraoperative high-dose rate of 32P brachytherapy in selected cases of recalcitrant diffuse conjunctival neoplasms. This technique offers a novel adjunct in the treatment of these cancers. Further follow-up and study are warranted.
Diffuse conjunctival cancers that are nonresectable are difficult to cure. Eradicating the lesion often destroys the normal function of these structures. Loss of the ocular surface can lead to loss of vision or the globe. Current eye-sparing treatments include surgery, cryotherapy, immunotherapy, chemotherapy, and radiation therapy. Surgical options are limited by the extent and location of the disease; larger lesions make complete resection impractical or ineffective because of the extent of specialized tissue that needs to be reconstructed. In squamous cell carcinoma of the conjunctiva, reports have shown that more advanced (T2-T3) tumors, classified using the American Joint Committee on Cancer clinical staging system, have higher recurrence rates after surgery.1 Topical chemotherapy and immunotherapy using mitomycin C, 5-fluorouracil, and interferon alfa-2b are widely used, with good results for tumor control (74% with mitomycin C; 72%-85% with interferon alfa-2b; and 57% with 5-fluorouracil); however, secondary complications and recurrences still occur.2-5 For diffuse or advanced disease or for those patients who fail both surgical and topical therapy, radiation therapy has been used to avoid extenteration. However, radiation techniques, such as external beam radiation, proton beam therapy, and brachytherapy, that have been used as adjuvant and definitive treatments for these diseases carry associated complications. Here, we present our experience with brachytherapy using a unique radioactive phosphorus (radioactive phosphorus 32 [32P])-impregnated flexible film for patients with recurrent diffuse conjunctival neoplasms. This technique allows a custom-sized, thin flexible film to be placed on the eye, delivering a full dose in 1 intraoperative treatment, providing a more localized delivery for select cases without the need for deeper orbital treatment.

Methods

This retrospective clinical research study was carried out with the permission of the institutional review board of Memorial Sloan-Kettering Cancer Center; the study was Health Insurance Portability and Accountability Act compliant. All patients provided oral consent. Patients with ophthalmic neoplasms treated with 32P were identified in the brachytherapy treatment–planning database. In all cases, a pathologist at our center confirmed the histopathologic diagnosis. Comorbidities were classified and scored according to the Adult Comorbidity Evaluation–27 scale. After treatment, patients were evaluated every 3 to 6 months to assess for local control and adverse events.

The brachytherapy film used for treatment was the RIC Conformal Source Model 100 (RIC-100, RI Consultants). The RIC-100 is a flexible, thin (approximately 0.5-mm) film made of a polymer chemically bound to 32P. Radioactive phosphorus 32 is an exclusive β emitter (<0.05% γ emission) with maximum energy of 1.71 MeV, average energy of 0.695 MeV, and half-life of 14.26 days. The maximum range is approximately 7 mm in water or biological tissues. The RIC-100 source has been approved by the US Food and Drug Administration as a single-use device and the cost at our center is just over $6000 for the source.

An ophthalmic oncologist and radiation oncologist evaluated patients jointly. Patients underwent mapping biopsies, as described by Putterman6 and detailed conjunctival drawings to delineate the pathologic extent of the disease. Cases selected for therapy had thin non-nodular tumors that were diffuse, covering a significant portion of the ocular and tarsal surface, or had multifocal or scleral recurrences. The gross tumor volume (GTV) consisted of clinically apparent neoplasm, and the clinical target volume (CTV) was the region adjacent to the GTV identified as abnormal by mapping biopsies and a 2-mm margin; this included the region proximal to the GTV in the case of negative mapping biopsies.

Under topical anesthetic, a flexible and transparent dummy film was cut to a custom size that encompassed the surface area and shape of the CTV, ensuring direct contact of the film on the surface of the conjunctiva (Figure 1A and B). A print of the dummy film was then sent to the supplier (RI Consultants) for fabrication of the radioactive 32P film. After fabrication, the 32P film was shipped to our institution. Prior to use, the radiation dose rate away from the film was measured and used to determine the duration of time necessary to deliver the prescribed total radiation dose at the prescription point (1 mm from the surface of the film).

Patients were brought to the operating room and general anesthesia was administered. Under sterile technique, the GTV and CTV were identified by the ophthalmic oncologist and radiation oncologist. The sterilized dummy film was positioned to confirm stability of the film in situ. The film was created to fit snugly in the fornices that secured it in position, similar to a scleral shell or conformer. Patient 4 required a limbal mattress suture to be preplaced to secure the smaller-sized film. After confirming acceptable positioning of the dummy film, attention was turned to the sterilized radioactive 32P film. The radioactive source was carefully removed from the shielded carrier with long smooth forceps and handled behind a 5-mm acrylic shield, avoiding abrasion, cutting, or grinding of the film. A wipe test was performed on the 32P film using a sterile cotton-tipped swab and analyzed in the operating room with a thin-windowed Geiger-Müller radiation detector. On confirming no residual radioactivity on the source, it was placed over the GTV and CTV (Figure 1C and D). After secure placement was confirmed, the eye was covered with wet towels, and operating room personnel increased their distance from the source to minimize radiation exposure. The film was left in place for the preplanned amount of time to deliver the prescription radiation dose.

After completion of brachytherapy (removal of the 32P film), the patient was surveyed for residual radioactivity in the operating room with a thin-windowed Geiger-Müller radiation detector. Occupational radiation dose measurements of the extremities were performed for the operating ophthalmologist and radiation oncologist using sterilized thermoluminescent dosimeters. The source characterization, in-hospital quality assurance procedures, and discussion of the clinical implementation and radiation safety precautions are described in detail by Cohen et al.7

Medical records were reviewed for ophthalmic adverse events, as defined by the Common Terminology and Criteria for
Results

Between January 1, 2010, and January 1, 2013, 7 eyes of 6 patients were identified and deemed eligible for study. Table 1 presents patient demographics, disease, treatment history, and comorbidities at the time of brachytherapy. The median age was 70 years (range, 51-80 years). All patients had a recurrent neoplasm. Most patients had squamous cell carcinoma of the conjunctiva that had recurred after a median of 3 prior therapies (range, 1-5).

Table 2 displays parameters of each course of brachytherapy. The median dose at the prescription point (1 mm from the surface of the film) was 15 Gy (range, 5-17 Gy). The median dose rate at the prescription point was 29 Gy per hour (range, 20-64 Gy/h). The median treatment time was 19 minutes (range, 10-52 minutes). The median film activity was 222 MBq (range, 50-277.5 MBq). The median film area was 5 cm² (range, 1-6.7 cm²). In some cases, radioactivity levels greater than the background count rate (50 cpm) were detected on removal of the ³²P film, as detected with the thin-windowed Geiger-Müller radiation detector in close proximity to the treatment site. After copious irrigation, levels returned to background counts per minute. Occupational radiation dose measurements of the extremities for the radiation oncologist and the ophthalmic oncologist did not exceed background radiation levels in 4 of the 7 cases. In cases in which the dose exceeded background radiation levels, the median net was 0.14 mSv (range, 0.014-0.04 mSv). No staff received excessive radiation doses.
The median follow-up was 24.9 months (range, 3.1-38.2 months). Recurrence-free survival 24 months after brachytherapy was 75% (95% CI, 19-89.1) (Figure 2) and was the same if we excluded patients with less than 24 months of follow-up. One patient experienced recurrence at eyelid margins and medial canthus as well as a perforated bacterial corneal ulcer 4.2 months after brachytherapy, which necessitated salvage orbital exenteration. This patient has been well controlled, with no evidence of disease recurrence since exenteration. No patients have developed scleral necrosis or metastases.

Table 3 presents the ophthalmic adverse events observed. Two moderate and 1 severe adverse event occurred. The former events were cataract development, which required surgery 29.8 and 7.6 months, respectively, after brachytherapy, which necessitated salvage orbital exenteration. This patient has been well controlled, with no evidence of disease recurrence since exenteration. No patients have developed scleral necrosis or metastases.

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Table 2. Brachytherapy Details, Follow-up, and Treatment Response

<table>
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<tr>
<th>Patient</th>
<th>Dose, Gy</th>
<th>Dose Rate, Gy/h</th>
<th>Treatment Duration, min</th>
<th>Activity, mCi</th>
<th>Film Area, cm²</th>
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</table>

* At prescription point, 1 mm from film surface.

Table 2. Brachytherapy Details, Follow-up, and Treatment Response

**Discussion**

Radiation has been used extensively for tumors in the head and neck region as well as eyelid neoplasms. β Radiation for the eye has been used since the 1930s when first reported by Moore using radon seeds for intraocular tumors. Since then, brachytherapy has been widely used for intraocular tumors and, to a lesser extent, conjunctival tumors. In a case series by Jones et al., eyes with conjunctival intraepithelial neoplasia were treated with a strontium-90 (90Sr) applicator to ocular surface lesions using 2 fractions of 1200 to 1524 cGy, totaling 2400 to 3050 cGy. There were no recurrences of the conjunctival intraepithelial neoplasia in the 4 cases over a 3-year follow-up, and the only reported complication was progression of cataract. Another study, using β radiation for conjunctival lymphoma using a 90Sr–yttrium-90 applicator, had an 87% control rate using 4000 to 8000 cGy divided into 500 to 2000 cGy weekly fractions. Their complications included cataracts in 15% and conjunctivitis and keratitis in 25%. The higher doses were associated with a greater incidence of adverse effects. Photon, proton, and electron beam radiation therapies have also been used for adjuvant and definitive treatment of conjunctival neoplasms. In a similar patient population to our study, external beam radiation was used to treat conjunctival squamous carcinoma. A control rate of 75% with doses of 50 to 60 Gy in 2.0- to 2.5-Gy daily fractions was obtained. In the 1 reported case of invasive conjunctival squamous carcinoma treated with proton beam radiation therapy, a dose of 3200 cGy was given in 4 fractions with local control for 9 months.

The adverse effects of radiation treatment of the eye have been well described and include cataract, dry eye syndrome, conjunctivitis, keratitis, glaucoma, scarring of the conjunctiva and cornea, episcleral telangiectasia or avascularity, conjunctival and scleral atrophy, keratinization of the conjunctiva, and poor wound healing. Rates of cataract with β radiation range from 21% to 45% and were found to be dose and loca-
tion dependent; with the $^{90}$Sr applicator, a dose greater than 5000 cGy was thought to cause cataracts.\textsuperscript{11,14,17}

The use of intraoperative $^{32}$P high-dose rate brachytherapy has been reported in brain and spinal tumors.\textsuperscript{18} This technique allowed an intraoperative adjunct to surgical resection or treatment of otherwise nonresectable lesions. Because of the film’s flexible nature, it conforms to specific areas during surgery and allows focal superficial treatment without damage to the underlying deep tissues. Local control rates of up to 80% have been obtained with this technique, even in lesions previously treated with radiation.\textsuperscript{18} Conjunctival lesions require the dose at the surface and not to the adjacent,

<table>
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<tr>
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<th>Grade 3</th>
<th>Grade 4</th>
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<tbody>
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<td>Patient No.</td>
<td>After Brachytherapy, mo</td>
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</tr>
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Abbreviation: NA, not applicable.

Figure 2. Clinical Photographs Before and After High-Dose Rate of Radioactive Phosphorus 32 ($^{32}$P) Brachytherapy

A. Pre-$^{32}$P brachytherapy of patient 1 showing squamous carcinoma involvement of the inferior fornix and cornea. B. Three years after with no recurrence. C. Pre-$^{32}$P brachytherapy of patient 4 showing recurrent squamous carcinoma in the cornea and sclera. D. Seven months later with no recurrence.
deeper, more sensitive tissues as with spinal lesions. The ability of the material to bend and its limited depth of penetration make it an ideal tool for treatment of diffuse conjunctival neoplasms without orbital disease. Another advantage of the technique is that it is completed in a single treatment, averaging 19 minutes, in a controlled operating room environment. The radiation doses chosen for treatment were based on the presumed radiosensitivity of the neoplasm harbored by the patient (lymphoma being most radiosensitive and requiring the lowest dose, and sebaceous carcinoma being the most radio-resistant and requiring the highest dose). In addition, the safety profile of other β-emitting isotopes frequently used on the conjunctiva (ie, 90Sr for pterygia) was considered when selecting the dose. A prospective clinical trial established that 25 Gy delivered at a high-dose rate in a single treatment for pterygia using 90Sr yielded no significant complications.19 The estimated median dose to the surface of the conjunctiva with the presently reported 32P brachytherapy technique is estimated to be 255% of the prescription dose 1 mm from the surface of the applicator, or 38.25 Gy for a 15-Gy prescription dose. The rapid radiation dose fall-off derived from β particles is likely responsible for the tolerability of this technique, but further studies are necessary to determine the optimal dose.

All of our cases were referred to us after having a biopsy or prior therapy elsewhere, and they had recurrent or residual disease. Only 1 eye, the second eye of the patient with lymphoma, had 32P treatment immediately after the initial biopsy because of the favorable results of the opposite eye. Most of the eyes (6 of 7) had failed multiple topical or surgical treatments before being treated with the 32P brachytherapy. All patients remained free of disease at last follow-up. The 1 case that recurred had advanced pagetoid spread of sebaceous carcinoma with involvement of 100% of the bulbar and tarsal conjunctiva. The nodular component was resected from the upper eyelid at the time of map biopsy, and a 32P plaque was placed to treat the entire conjunctiva. The patient developed a bacterial corneal ulcer with perforation. The patient was treated for the ulcer, and repeat map biopsies showed recurrent disease at the eyelid margins and caruncle. It was decided at that time to proceed with an exenteration, and the patient has been disease free without systemic spread. It is possible that one reason for recurrence was the type of cancer because all other successful cases were not sebaceous carcinoma. Another reason may be related to the large GTV, in that possible occult eyelid margin disease and caruncle disease received less of a dose owing to their location being further from the radiation source.

Our treatment adverse effects included 2 grade 1 ocular surface symptoms and 2 grade 3 cataracts that required treatment following brachytherapy; however, both of these patients had significant cataracts that were not treated prior to the 32P brachytherapy because of the underlying active neoplasm. The grade 4 adverse effect was discussed here with the case of recurrence (Table 3). The adverse effects were comparable with those of the already-referenced series. Despite some of the adverse events, final vision remained equal or better than 20/40 in 5 of the 7 eyes.

Conclusions

Our results show the use of an intraoperative high-dose rate of 32P brachytherapy in selected cases of diffuse conjunctival neoplasms. The technique was used for diffuse neoplasia in contrast to thick nodular disease or cases with suspected orbital disease and showed its best preliminary results with limited complications in cases of squamous cell carcinoma. This technique offers an additional, novel approach for the treatment of select diffuse conjunctival neoplasms. The study was limited by its retrospective nature, limited follow-up in some cases, and a small number of patients, which resulted in wide confidence intervals regarding results presented. Additional cases and continued follow-up of this technique need to be explored, along with the investigation of other potential applications.


