

# Exposure of Primary Orbital Implants in Postenucleation Retinoblastoma Patients

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**Purpose:** To determine significant factors influencing the exposure of primary orbital implants in patients with retinoblastoma.

**Design:** Retrospective noncomparative case series.

**Participants:** One hundred nine consecutive patients (110 sockets) who had undergone enucleation for retinoblastoma from January 1993 to December 1997.

**Methods:** Two patients with recurrence of orbital retinoblastoma were excluded from further analysis, leaving 107 patients (108 sockets). The parameters analyzed included the patient's age; gender; ocular diagnosis; surgeon; type, covering, and size of the implant; the use of chemotherapy or radiotherapy; and the timing of these treatments in relation to enucleation. Study patients were divided into two main groups: the "treated group"—patients who had undergone adjuvant external beam radiotherapy or chemotherapy, and the "untreated group"—patients had undergone enucleation with or without cryotherapy, laser thermotherapy, or brachytherapy to the index or fellow eye. The following additional parameters were noted in the patients with exposed implants: time to exposure from date of enucleation and treatment of exposure.

**Main Outcome Measure:** Exposure of orbital implants.

**Results:** There were two exposures caused by orbital recurrence of retinoblastoma. The rate of nontumor recurrence exposure was 28% (30 of 108). The median time to exposure was 136 days (range, 1–630 days). There were 18 exposures (35%, 18 of 51) in the treated group, with a 34% exposure rate (13 of 38) in the chemotherapy group. The exposure rate was 21% (12 of 57) in the untreated group. The rates of exposure according to implant were: Vicryl mesh-wrapped hydroxyapatite (2 of 18, 11%), Medpor (8 of 13, 53%), plain polymethylmethacrylate (PMMA) (4 of 50, 8%), Mersilene-wrapped PMMA (9 of 17, 53%) and Castroviejo (7 of 10, 70%). Eight of the exposures (27%) were managed conservatively; the remainder required surgical repair.

**Conclusions:** Results suggested that implant type and covering ( $P = 0.000$ ) had a highly significant effect on the rate of exposure in postenucleation retinoblastoma patients. There was no statistical evidence that age, gender, ocular diagnosis, surgeon, size of the implant, or radiotherapy had an effect on implant exposure. There was an increased rate of exposure in the chemotherapy group, although this did not achieve statistical significance ( $P = 0.058$ ), but a detrimental effect could not be excluded. *Ophthalmology* 2000;107:940–946 © 2000 by the American Academy of Ophthalmology.

The goal of enucleation of an eye with retinoblastoma and insertion of a primary orbital implant is to remove the diseased globe, to stop extraocular spread, and to provide acceptable cosmesis. Clinical management of retinoblastoma is changing with the advent of new integrated implants and the increasing use of chemotherapy.<sup>1–4</sup> We have noted a significant number of exposures of primary orbital implants

in postenucleation retinoblastoma patients. This study attempts to identify any causes of this phenomenon during this period of transition.

## Methods

The Ocular Oncology Service is the major tertiary referral center for retinoblastoma in England. One hundred nine records (110 sockets) of consecutive patients who had undergone enucleation for retinoblastoma from January 1993 to December 1997 with a minimum of 3 months follow-up were available for review. Before January 1993, chemotherapy had usually been reserved for advanced intraocular<sup>1</sup> and extraocular disease; after this date, chemotherapy became gradually more widely used as a first-line treatment for intraocular disease.

## Protocols of Patient Follow-Up

When the patients underwent external beam radiotherapy, they were followed up with an examination under anesthesia 6 to 8 weeks after the initial radiotherapy, then every three months until

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the age of 2, and then every four months from the age of 2 to 4. After the age of 4, they would usually be examined awake in the clinic. Patients undergoing chemotherapy had examinations done under anesthesia after every two cycles of chemotherapy until the end of the treatment regimen, when they would proceed with the follow-up arrangements according to age, as detailed previously. If a patient had undergone treatment for a relapse or new tumor, an examination with the patient under anesthesia would be arranged 1 month after the treatment.

## Treatment for Retinoblastoma

Enucleation was undertaken as a primary treatment if there was anterior segment involvement by tumor or if there was extensive vitreous disease at presentation and after the failure of conservative treatment. Other treatment modalities included cryotherapy, thermotherapy, brachytherapy, and external beam radiotherapy (using the whole eye or a lens-sparing technique).

Chemotherapy was used as first-line treatment for intraocular disease since January 1993. The first-line regimen was JOE (consisting of vincristine, etoposide, and carboplatin), described in an earlier publication.<sup>1</sup> After January 1993, most patients with bilateral retinoblastoma had chemotherapy initiated within days of the enucleation of the fellow eye. They normally underwent six to eight courses of chemotherapy at 3-week intervals to allow for the recovery of the platelet count between the courses. Chemotherapy was also begun after a report of adverse histologic findings in the enucleation specimen. This included extension of the tumor beyond the cut end of the optic nerve, deep choroidal invasion, or extrascleral extension. These patients usually underwent four courses of adjuvant JOE chemotherapy. Second-line chemotherapy was initiated for a variety of indications—the most common being vitreous relapse in an eye after the patient had already undergone the JOE regimen earlier in the treatment.

## Treatment Undertaken for Exposure

*Conservative treatment* consisted of topical antibiotics and modification of the prosthesis, generally with increased vaulting of the posterior surface. *Resuturing of conjunctival dehiscence*: the wound was revised by mobilizing all anterior adhesions to the exposed implant and resuturing with generous closure of Tenon's capsule and the conjunctiva in two separate layers. *Implant exchange*: The exposed implant was replaced with a buried nonintegrated plain polymethylmethacrylate (PMMA) sphere with no rectus attachments. *Removal of implant*: An implant was replaced only in cases in which there was significant fibrosis causing contracture or pre-existing infection, causing a high risk of exposure in the new implant, or when there had been a history of recurrent implant exposures. *Excision of suture granulomas*: suture granulomas were excised because they caused poor fitting of the prosthesis and the wound resutured.

**Parameters.** The parameters included the patient's age at enucleation, ocular diagnosis (unilateral or bilateral, sporadic, or familial), type (Castroviejo, Medpor, hydroxyapatite, or PMMA) and covering of the implant (Mersilene mesh, Vicryl mesh, or none), size of the implant, the surgeon, use of chemotherapy or radiotherapy, and timing of these treatments in relation to enucleation. In the group of patients with exposed implants, the following were noted: time to first signs of exposure from date of enucleation, any cause for exposure, and treatment of exposure. The sockets were divided into two main groups. The first group consisted of untreated sockets (these included patients who had previously undergone cryotherapy, thermotherapy, or brachytherapy (it was calculated that orbital tissue receives 0 to 200 cGy in a properly shielded iodine plaque so effects of orbital radiation from

brachytherapy should be minimal.)<sup>9</sup>; and those who had orbital implant exposure develop before their chemotherapy or radiotherapy (because these treatments could not have been a factor influencing exposure). The second group consisted of treated sockets: patients who had undergone chemotherapy and/or "received 4000 to 5000 cGy in external beam radiotherapy before or at the time of exposure." Because we were specifically concerned about the effects of chemotherapy, we also analyzed our results with regard to a "chemotherapy sockets" group within this second set of patients.

## Statistical Methods

The outcome was defined as "exposed" or "not exposed." All data were described as the median and range. The chi-squared test or the Fisher's exact test was used for categorical data. Quantitative data such as age were analyzed by use of a rank sum test.  $P \leq 0.05$  was considered significant. Factors found to be significant on univariate analysis were entered into a linear logistic regression.

## Enucleation Technique

All the enucleations were performed by surgeons in the Ocular Oncology Service and all used the technique detailed later, which had been consistent over this period. The surgery was performed with the patient under general anesthesia. We first made a 360-degree peritomy at the limbus. The Tenon's fascia was divided using blunt dissection in all four quadrants to isolate the rectus muscles, which were then hooked and tagged with 5/0 catgut sutures before they were cauterized and cut near to the insertion leaving a 1-mm stump. The stump was then anchored with a 4/0 silk suture on a cutting needle, avoiding penetration of the globe. The oblique muscles were hooked, cauterized, and then cut. The silk sutures from the stumps of the four recti were then gathered and twisted together and clipped by an artery forceps to allow even distribution of tension on the globe. The globe was gently maneuvered out of the socket to allow the insertion of a snare, which was introduced as posteriorly as possible into the orbit to obtain a good length of optic nerve. The snare was tightened to cut the nerve and the globe was removed. The socket was firmly compressed with wet gauze and digital pressure for 5 to 10 minutes for hemostasis. All implants were placed as far posteriorly as possible in the muscle cone. This was facilitated by the use of a strip of plastic drape as a tubular sheath for the introduction of the implant to prevent dragging of the Tenon's capsule. With implants to which the recti could be sutured, the muscle attachments were anteriorized so that thick and more viable layers of Tenon's capsule and conjunctiva could be meticulously closed in two separate layers. We generally put in the largest implant (84% of the implants were 16 mm or more) over the conjunctiva, and the Tenon's could be closed adequately to avoid replacement of the implant with orbital growth.

*Plain PMMA sphere (baseball implant)*: The rectus muscles were not attached to this implant. *Mersilene-wrapped PMMA sphere*: The recti were advanced 3 to 5 mm from the apex of the implant and sutured onto the mesh. *Castroviejo implant*: The recti were sutured onto the anterior haptens. *Vicryl mesh-wrapped hydroxyapatite*: The implant was left spherical and not modified. The recti were attached in an anteriorized position described earlier. None of our patients have undergone pegging of their hydroxyapatite implants. *Medpor* (Porex Surgical Inc, Georgia): Four small grooves were made at the apex of the implant with a Bard-Parker blade to allow for the suturing of the recti directly onto the implant. No covering was used with this implant, as recommended by the manufacturer.

Table 1. Types of Implants and Exposure Rates

| Implant                    | Treated   |         | Chemotherapy |         | Untreated |         | Rate of Implant Exposure | Odds Ratio for Exposure Compared with PMMA |
|----------------------------|-----------|---------|--------------|---------|-----------|---------|--------------------------|--|
|                            | Unexposed | Exposed | Unexposed    | Exposed | Unexposed | Exposed |                          |  |
| Castroviejo                | 0         | 4       | 0            | 3       | 3         | 3       | 70% (7/10)               | 20.7 (P = 0.001)                           |
| Medpor                     | 1         | 6       | 1            | 5       | 4         | 2       | 62% (8/13)               | 12.0 (P = 0.003)                           |
| Baseball                   | 21        | 1       | 14           | 1       | 25        | 3       | 8% (4/50)                |  |
| Mersilene/baseball         | 3         | 5       | 8            | 2       | 5         | 4       | 53% (9/17)               | 16.0 (P = 0.00)                            |
| Hydroxyapatite/Vicryl mesh | 8         | 2       | 2            | 2       | 8         | 0       | 11% (2/18)               | 1.10 (P = 0.93)                            |
| Total                      | 33        | 18      | 25           | 13      | 45        | 12      | 28% (30/108)             |  |

PMMA = polymethylmethacrylate.

A conformer was placed between the lids and the bulbar conjunctiva, and a firm pressure bandage was applied overnight. The patient was normally reviewed in clinic on the first postoperative day and 3 weeks after surgery to evaluate the wound and histologic findings of the enucleated specimen. The patient was referred to an ocularist 4 to 6 weeks after enucleation, when measurements were taken for a permanent prosthesis. A temporary prosthesis was supplied in the interim. None of our patients in this series has had peg placement of their Medpor or hydroxyapatite implants.

## Results

One hundred nine records were reviewed (110 sockets). There were 55 males and 54 females. There were 48 right eyes and 62 left eyes. The median age at diagnosis was 19.0 months (range, birth–136 months). The median age at enucleation was 24.0 months (range, 1.0–154 months). The frequency of various orbital implants and their sizes, ocular diagnosis, and gender with respect to exposure rate are shown in Tables 1 to 4. The median follow-up was 21.6 months (range, 3.0–55.0 months) after enucleation.

## Patient Treatment

The two patients (one male and female) with orbital retinoblastoma causing secondary exposure of the implants were excluded from further statistical analysis. There were 50 patients (51 sockets) in the treated group. Of these, 13 patients (14 sockets) underwent enucleation with adjuvant chemotherapy and external beam radiotherapy, 23 (24 sockets) had only adjuvant chemotherapy, and 12 (13 sockets) had only adjuvant radiotherapy. There were 57 patients (57 sockets) in the untreated group. There were three patients (three eyes) in the untreated group who had undergone plaque brachytherapy, whereas in the treated group seven patients (eight eyes) had undergone plaque brachytherapy.

## Rates of Exposure in Treated and Untreated Sockets

A total of 30 patients (30 sockets, 28%) had exposure of their orbital implants. There were 18 females and 12 males. Twelve (40%) patients had symptoms of excessive discharge from the socket. There was a 35% (18 of 51) exposure rate in the treated group (with 13 of 38 [34%] exposures in the chemotherapy group). There was a 20% (12 of 57) exposure rate in the untreated group.

## Timing of Exposure

In the untreated socket group, the median time from enucleation to exposure was 153 days (range, 1–630 days). In the treated socket group, the median time was 118 days (range, 19–544 days). Two patients in each group had implant exposure in the first 30 days after surgery. Eighty seven percent of all exposures (26 of 30) occurred in the first year after enucleation.

## Management of Exposed Implant

In the untreated socket group, two resolved with conservative management, six were resutured, and four patients required implant exchange. In the treated socket group, four resolved with conservative management, four were resutured, and 10 required eventual implant removal. Two patients with conjunctival thinning but no actual implant exposure underwent removal of the original implant and replacement with a hydroxyapatite implant because of problems of fitting a prosthetic eye. Five of the seven exposed Castroviejo implants needed to be removed. Three of the exposed plain PMMA implants were managed conservatively, and one was removed. Four of the Mersilene-wrapped PMMA implants were resutured, four were removed, and one exposure resolved after conservative treatment. Both hydroxyapatite implants were resutured. Of the Medpor implants, four were resutured, two were removed, and two were exchanged.

Table 2. Exposure of Different Sizes of Implant

| Implant Size (mm)      | Treated   |         | Chemotherapy |         | Untreated |         |
|------------------------|-----------|---------|--------------|---------|-----------|---------|
|                        | Unexposed | Exposed | Unexposed    | Exposed | Unexposed | Exposed |
| 14                     | 2         | 1       | 1            | 0       | 2         | 0       |
| 16                     | 17        | 7       | 13           | 5       | 20        | 5       |
| 18                     | 9         | 3       | 9            | 2       | 17        | 2       |
| 20                     | 1         | 1       | 0            | 1       | 2         | 0       |
| Castroviejo (one size) | 0         | 4       | 0            | 3       | 3         | 3       |
| Not recorded           | 4         | 2       | 2            | 2       | 1         | 2       |

Table 3. Implant Exposure According to Diagnosis

| Diagnosis                          | Total | Not Exposed | Exposed |
|------------------------------------|-------|-------------|---------|
| Unilateral sporadic retinoblastoma | 70    | 52          | 18      |
| Unilateral familial retinoblastoma | 2     | 0           | 2       |
| Bilateral sporadic retinoblastoma  | 33    | 23          | 10      |
| Bilateral familial retinoblastoma  | 3     | 3           | 0       |

### Factors Influencing the Rate of Exposure

Results suggested that implant type and covering affected exposure rate ( $P = <0.001$ ), but age at enucleation, sex, diagnosis, surgeon, implant size, and radiotherapy appeared not to have an effect on implant exposure. There was an increased rate of exposure (34%) in the chemotherapy group compared with that (21%) in the untreated group. This did not reach statistical significance on multivariate analysis ( $P = 0.058$ ).

### Discussion

As far as we are aware, this is the largest study examining the rate of exposure of primary implants in retinoblastoma patients. Enucleation is often the definitive treatment of large unilateral retinoblastomas, the worse eye in bilateral disease, and relapsed eyes after failure of other treatment modalities. The aim of insertion of an orbital implant is to replace lost orbital volume. This improves cosmesis and prosthesis motility. In the Ocular Oncology Unit at St. Bartholomew's, our practice has evolved with the increasing choice of different implants and covering. We have consistently avoided using donor sclera, taking into account the United Kingdom Health Service Guidelines.<sup>5</sup>

Current management of retinoblastoma involves a multimodal approach incorporating enucleation, cryotherapy, laser thermotherapy, plaque brachytherapy, external beam radiotherapy, and chemotherapy. Survival rates are in excess of 90%, but the burden of coping with permanent visual and systemic morbidity often remains, especially in those with bilateral and/or familial disease. Previously, chemotherapy had been used only in the treatment of relapse after radiotherapy or extraocular extension of the disease, but in recent years, chemotherapy has been widely used with other modalities in the treatment of intraocular disease.<sup>6,7</sup> This has decreased the risk of cosmetic and functional deformities associated with radiation therapy, but the long-term effects have not yet been determined. We were concerned whether the new therapeutic approach of different implants and increasing use of chemotherapy may have an effect on the rate of exposure.

### Type and Covering of Orbital Implant

Results from this study strongly suggest that the main factors influencing exposure are the type and covering of the implant. The search for an ideal orbital implant has evolved over the years. The anophthalmic orbit is physiologically and anatomically different, with decreased metabolic activity and vascularity as demonstrated by thermography,<sup>8</sup> and the tissues undergo trophic changes. Orbital implants have been shown to be beneficial to orbital growth<sup>9</sup> in addition to replacing the volume of the enucleated eye and promoting prosthesis motility.

Both hydroxyapatite and plain PMMA implants appear to have lower exposure rates in the pediatric orbit, whereas Medpor, Mersilene-wrapped PMMA, and Castroviejo implants have a greater than 50% exposure rate in our study. The hydroxyapatite implant offers the option of drilling and peg placement for better prosthesis mobility at a later stage and has become the implant of choice in many centers.

We have been using the baseball implant for many years with excellent results, as have other clinicians using this implant. Shields et al<sup>10</sup> reported no complications in a series of more than 1000; others noted extrusion rates of 4%.<sup>11</sup> However, it is interesting that wrapping the same implant in Mersilene mesh to allow attachment of the recti causes a much higher rate of exposure. This may have resulted from the rough surface of the Mersilene mesh causing mechanical irritation and subsequent exposure. The Castroviejo implant also had unfavorable results in our series. It is interesting to speculate why high-density porous polyethylene or Medpor, with a long successful history in facial reconstructive procedures<sup>12</sup> and with excellent results reported in adult enucleations,<sup>2</sup> should have such a high rate of exposure in the pediatric retinoblastoma orbit. This is particularly marked in the "chemotherapy socket" group, with exposures of 86% (5 of 6). Our experience is similar that of Karcioğlu and coworkers,<sup>13</sup> who also found this unwrapped implant to have a high rate of exposure (21.6%) in a series of 34 retinoblastoma patients. Our results with Vicryl mesh-wrapped hydroxyapatite have been encouraging, although the numbers included in this study are still relatively small. This implant of inorganic salt, first described by Perry,<sup>3</sup> is our current porous implant of choice. Vicryl mesh (polyglactin 910) is an absorbable synthetic copolymer, which is nonantigenic, nonpyogenic, inexpensive, and elicits only a mild tissue reaction clinically.<sup>14</sup> Studies have demonstrated variable success of hydroxyapatite implants with exposure rates for this implant varying from 1% to 28%.<sup>15</sup> Shields & coworkers,<sup>16</sup> in the largest series to date of 250 enucleations (70 for retinoblastoma), had one infection and four exposures (1.6%), which were all in children.

Table 4. Gender and Exposure Rate

| Gender | Exposed | Unexposed | Treated Unexposed | Treated Exposed | Untreated Unexposed | Untreated Exposed |
|--------|---------|-----------|-------------------|-----------------|---------------------|-------------------|
| Male   | 54      | 12        | 42                | 21              | 9                   | 3                 |
| Female | 53      | 18        | 35                | 11              | 9                   | 9                 |
| Total  | 107     | 30        | 77                | 32              | 18                  | 12                |

In a prospective study from the same unit of 60 pediatric patients, 51 with retinoblastoma, de Potter et al<sup>4</sup> found no actual exposure in their series. Dutton<sup>17</sup> reported no complications in a series of 50. Buettner and Bartley<sup>18</sup> observed a 22% exposure. Many authors believe that healing is difficult once hydroxyapatite is exposed in the early stages because complete vascularization takes between 6 and 10 months. Some authors have suggested drilling holes to the center of the implant to expedite this process.<sup>19</sup> Reznick and Gilmore<sup>20</sup> have suggested that this implant, despite its chemical similarities to the inorganic bone matrix, behaves like a foreign body in infection. The central unvascularized core can act as a harbor for organisms, leading to chronic fistulization.<sup>21</sup> Misiek and colleagues<sup>22</sup> have also suggested that the degree of microscopic coarseness of the pores may predispose to exposure.

### Timing of Exposure

Causes of orbital implant extrusion can be divided into early and late.<sup>23,24</sup> Early extrusion could be caused by edema, infection, hemorrhage, too large an implant or conformer, or faulty surgical technique. In the mainly adult-based literature, most implants expose in the first 16 weeks in the postoperative period.<sup>18,21,25</sup> Goldberg et al<sup>26</sup> had six hydroxyapatite implants exposed within 4 to 6 weeks after enucleation. A small proportion (13%, 4 of 30) of our exposures occurred in the first 30 days after enucleation. Eighty-seven percent (26 of 30) of our exposures occurred in the first year after enucleation.

Friction from a poorly fitting prosthesis may lead to erosion of tissue covering the anterior surface of the implant, leading to late extrusion. This can be due to pressure necrosis with secondary infection or conjunctival downgrowth through the dehiscence. Conjunctival downgrowth may cause epithelialization of the cavity around the implant, with resulting contracture of the orbital tissues.<sup>27</sup> To ensure a good prosthetic fit in a young child, we occasionally undertake molding under anesthesia. Late exposure may also be influenced by orbital growth and remodeling in the pediatric orbit.

### Effect of Chemotherapy and Radiotherapy on Exposure Rate

We have similar findings as previous experimental studies that preimplantation radiotherapy does not appear to have a detrimental effect on the retention of primary orbital implant.<sup>28</sup> There is an increased rate of exposure in the chemotherapy group, 34% compared with 21% in the untreated group, although this does not attain statistical significance ( $P = 0.058$ ). However, this study has the limitation of retrospective analysis, with all the resulting difficulties of drawing conclusions from a large series of patients treated with different methods. The ideal would be prospective randomized study of orbital implants in chemotherapy sockets, but to obtain the number of patients necessary in these complicated cases would be impracticable as well as unethical because it would involve jeopardizing patient care by withholding adjuvant treatment from some groups.

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