Objective: To evaluate irradiation toxic effects from fluoroscopy during intra-arterial chemotherapy for retinoblastoma.

Design: Prospective trial.

Participants: Eight patients treated with intra-arterial chemotherapy.

Main Outcome Measures: Irradiation toxic effects in vital organs.

Results: The mean patient age was 29 months (range, 10-74 months) and 63% were male. The mean irradiation dose to the skin of the affected eye was 0.19173 Gy, to the contralateral eye was 0.03533 Gy, to the chest wall was 0.00296 Gy, and to the abdominal wall was 0.00104 Gy. The estimated irradiation dose to the lens in the treatment eye was 0.16 Gy, which, in accumulated doses, could be cataractogenic. The estimated irradiation dose from a single fluoroscopy session to other organs, including the brain (0.05560 Gy), thyroid (0.00192 Gy), bone marrow (0.00059 Gy), and gonads (0.00015 Gy), was far lower than the minimal toxic level.

Conclusions: Careful use of fluoroscopy during intra-arterial chemotherapy with limited irradiation exposure is advised. Accumulated irradiation toxic effects following multiple sessions of intra-arterial chemotherapy could be cataractogenic and possibly carcinogenic, especially in irradiation-sensitive patients with retinoblastoma.
patients who did not receive irradiation. The incidence rate of second cancers in patients with retinoblastoma was 35.1% for patients who received standard external beam radiotherapy compared with an incidence rate of 5.8% for patients who did not receive irradiation. Wong and coworkers\(^5\) determined the dose-response relation for soft tissue sarcoma and irradiation dose in patients with retinoblastoma. They also did not note any sarcomas at an irradiation exposure from fluoroscopy in children with retinoblastoma. The cumulative irradiation exposure at the skin level for each patient, the dosimeters were placed at the lateral canthus of each eye, thorax (placed on the midaxillary line at the level of the nipples), and abdomen (over the umbilicus). The dosimeter values were calculated per each catheterization and the individual organ irradiation exposure was estimated based on previous reports of organ toxic reaction.\(^6\)-\(^10\)

Patients with retinoblastoma treated with intra-arterial chemotherapy had previously received systemic chemotherapy and local cryotherapy. The clinical features of the tumors are listed in Table 1. The stage of tumor according to International Classification of Retinoblastoma was group A (n=0), group B (n=0), group C (n=1; 12\%), group D (n=0), group E (n=5; 64\%), and recurrent tumor (n=2; 24\%). The mean tumor basal dimension was 18 mm (median, 18 mm; range, 10-22 mm) and the mean thickness was 8 mm (median, 8 mm; range, 3-13 mm). Subretinal seeds were seen in 5 patients (63\%) (focal seeds in 1 [13\%] and diffuse seeds in 4 [50\%]). Vitreous seeds were seen in 7 patients (88\%) (focal seeds in 1 [12\%] and diffuse seeds in 6 [76\%]). The mean height of the patients was 88 cm (median, 87 cm; range, 74-116 cm) and the mean weight was 13 kg (median, 12 kg; range, 8.2-22 kg). The irradiation exposure to each anatomic site is listed in Table 2. The maximum irradiation exposure was to the treatment eye, at a mean of 0.19173 Gy (median, 0.16840 Gy; range, 0.06235-0.46611 Gy). The irradiation exposure to the contralateral eye was approximately 5 times less compared

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**Table 1. Demographic and Tumor Features of 8 Patients With Retinoblastoma Treated With Intra-arterial Chemotherapy**

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. (%) (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation, mo, mean; median (range)</td>
<td>29; 23 (10-74)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>5 (63)</td>
</tr>
<tr>
<td>F</td>
<td>3 (37)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7 (88)</td>
</tr>
<tr>
<td>African American</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Eye affected</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>3 (37)</td>
</tr>
<tr>
<td>Left</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Bilateral retinoblastoma</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Family history of retinoblastoma</td>
<td>0</td>
</tr>
<tr>
<td>International Classification of Retinoblastoma</td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>0</td>
</tr>
<tr>
<td>Group B</td>
<td>0</td>
</tr>
<tr>
<td>Group C</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Group D</td>
<td>0</td>
</tr>
<tr>
<td>Group E</td>
<td>5 (64)</td>
</tr>
<tr>
<td>Recurrent tumor</td>
<td>2 (24)</td>
</tr>
<tr>
<td>Tumor features</td>
<td></td>
</tr>
<tr>
<td>Tumor basal diameter, mm, mean; median (range)</td>
<td>18; 18 (10-22)</td>
</tr>
<tr>
<td>Tumor thickness, mm, mean; median (range)</td>
<td>8; 8 (3-13)</td>
</tr>
<tr>
<td>Subretinal seeds</td>
<td></td>
</tr>
<tr>
<td>No subretinal seeds</td>
<td>3 (37)</td>
</tr>
<tr>
<td>Focal subretinal seeds</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Diffuse subretinal seeds</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Vitreous seeds</td>
<td></td>
</tr>
<tr>
<td>No subretinal seeds</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Focal subretinal seeds</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Diffuse subretinal seeds</td>
<td>6 (76)</td>
</tr>
</tbody>
</table>
with the treatment eye, averaging to 0.03533 Gy (median, 0.02599 Gy; range, 0.00578-0.10292 Gy). This irradiation exposure decreased progressively according to distance from the treatment eye and was approximately 65 times less at the level of the thorax (mean, 0.00296 Gy; median, 0.00049 Gy; range, 0.00023-0.00138 Gy). The irradiation exposure decreased further at the level of the umbilicus, amounting to approximately 184 times less compared with the treatment eye (mean, 0.00104 Gy; median, 0.00077 Gy; range, 0.00033-0.00435 Gy).

Using previous studies, the correlation between skin entrance dose and organ toxic reaction can be calculated.6-10 (The percentage of organ irradiation dose to the skin dose was calculated from the reported values in the previous studies.) Though this is only an approximation, it provides a reasonable estimate of irradiation exposure to internal organs. The irradiation dose to the lens was approximately 87% of the ipsilateral lateral canthus skin dose, dose to the brain was 29% of the lateral canthus skin dose, dose to the thyroid gland was 65% of the midsternal chest wall skin dose, dose to the bone marrow was 20%, and dose to the gonads was 14% of the abdominal umbilicus skin irradiation dose.6-10

Using these organ dose approximations, the internal organ exposure was calculated and is represented in Table 3.

The average irradiation dose to the lens in the treatment eye was 0.16681 Gy and to the contralateral eye was 0.03074 Gy. The average dose to the brain was 0.05560 Gy, to the thyroid gland was 0.00192 Gy, to bone marrow was 0.00059 Gy, and to the gonads was 0.00015 Gy.

The mean follow-up time after intra-arterial chemotherapy was 4 months (range, 1-6 months). During the follow-up, no lens changes were witnessed in any of the patients. Only 1 patient underwent enucleation during the follow-up period and pathology results did not show any cataractous changes.

**Table 2. Cutaneous Irradiation Exposure During 11 Sessions of Intra-arterial Chemotherapy**

<table>
<thead>
<tr>
<th>Site of Exposure as Measured by microStar Radiation Dosimetersa</th>
<th>Irradiation Level, Gy (N=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment eye Mean</td>
<td>0.19173</td>
</tr>
<tr>
<td>Median (range) Mean</td>
<td>0.16840 (0.06235-0.46611)</td>
</tr>
<tr>
<td>Contralateral eye Mean</td>
<td>0.03533</td>
</tr>
<tr>
<td>Median (range) Mean</td>
<td>0.02599 (0.00578-0.10292)</td>
</tr>
<tr>
<td>Thorax Mean</td>
<td>0.00296</td>
</tr>
<tr>
<td>Median (range) Mean</td>
<td>0.00245 (0.00114-0.00790)</td>
</tr>
<tr>
<td>Abdomen Mean</td>
<td>0.00104</td>
</tr>
<tr>
<td>Median (range) Mean</td>
<td>0.00077 (0.00033-0.00435)</td>
</tr>
</tbody>
</table>

a Manufactured by Landauer, Glenwood, Illinois.

There are numerous terms to describe irradiation dose to human tissue, including background equivalent radiation time (BERT), critical organ dose (COD), dose area product (DAP), diagnostic acceptable reference level (DARling), effective dose (ED), fetal absorbed dose (FAD), total imparted energy (TIE), and surface absorbed dose (SAD).13 Surface absorbed dose, which is also known as entrance skin dose, is the amount of energy imparted per gram of tissue at the entrance surface.10 The European Union has identified surface absorbed dose as the diagnostic reference parameter in optimizing irradiation dose17 and was therefore used as the measurement for irradiation dose in this study.

Irradiation imaging of pediatric patients is unique in that the tissues are more radiosensitive in this population and there is a longer lifetime for irradiation-related cancer.18 Data from atomic bomb survivors have been pivotal in the understanding of irradiation carcinogenesis. Individuals exposed 50 years ago to doses comparable with those associated with helical computed tomography today show a small but statistically significant increased incidence of cancer. Using this information, a child undergoing an abdominal helical computed tomographic scan has a lifetime risk of fatal cancer approximately 1 in 1000.19 Brenner and coworkers20 reported that the estimated lifetime cancer mortality risks attributable to the irradiation exposure from computed tomography in a 1-year-old are 0.18% (abdominal) and 0.07% (head). Keeping in mind the potential toxic effects of pediatric irradiation exposure, the principle of “As Low As Reasonably Achievable” (ALARA) should be exercised to minimize irradiation dose.

The crystalline lens is one of the most radiosensitive tissues in the body.21 Recent studies indicate that the threshold for cataract development is less than was previously estimated and is approximately 0.5 Gy.11 The re-

**Table 3. Estimated Organ Irradiation Dose During 11 Sessions of Intra-arterial Chemotherapy**

<table>
<thead>
<tr>
<th>Approximate Organ Doseb,f</th>
<th>Estimated Irradiation Dose, Gy (N=11)</th>
<th>Established Irradiation Dose Toxic Level Harmful to the Organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lens</td>
<td>Treatment eye</td>
<td>0.5 Gy11</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.16681</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.14651 (0.05424-0.40552)</td>
<td>0.5 Gy11</td>
</tr>
<tr>
<td>Contralateral eye</td>
<td>Treatment eye</td>
<td>50-60 Gy12</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.02261</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.00192</td>
<td></td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>Bone marrow</td>
<td>2 Gy14</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.04884 (0.01808-0.13517)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.00159</td>
<td></td>
</tr>
<tr>
<td>Medial (range)</td>
<td>0.00015</td>
<td></td>
</tr>
<tr>
<td>Gonads</td>
<td>Treatment eye</td>
<td>2 Gy14</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.00011 (0.00005-0.00061)</td>
<td></td>
</tr>
</tbody>
</table>

b Superscripts represent the reference number from which the toxic level for the organ was obtained.
risk coefficients of any organ and is the only solid organ
therapy is well below the toxic level and therefore likely
failing second cancers. Also, the age of the patient prior to
toma with hereditary mutation causing susceptibility to
in cell culture studies.23,24 Marees and associates25 re-
irradiation has been demonstrated and well documented
effects.

The thyroid gland in children has one of the highest
risk coefficients of any organ and is the only solid organ
tissue with convincing evidence for risk at about 1.1 Gy.13
The thyroid irradiation dose in our study was a mean of
0.002 Gy with a maximum level of 0.005 Gy, which is
lower than the toxic dose to pediatric thyroid tissue. Ron
and coworkers11 also suggested that spreading the dose
over time (from a few days to >1 year) may lower risk,
possibly because of the opportunity for cellular repair
mechanisms to operate. The average interval between in-
tra-arterial procedures is 4 weeks and this could aid in
minimizing organ irradiation toxic effects.

The bone marrow and gonads are other structures that
have an increased sensitivity to irradiation, particularly
in growing children.18 In our study, the average irradia-
tion dose to bone marrow was 0.0006 Gy (maximum,
0.00158 Gy) and to the gonadal tissue was 0.0002 Gy
(maximum, 0.0061 Gy). The irradiation level above
which toxic effects appear for bone marrow is 2 Gy and
for gonads is 2 Gy.13,14 The irradiation dose to these
organs in this study was far lower than the level of toxic
effects.

The increased sensitivity of retinoblastoma cells to ir-
radiation has been demonstrated and well documented
in cell culture studies.23,24 Marees and associates25 re-
ported that the cumulative mortality from any second ma-
lignancy 50 years after retinoblastoma diagnosis was 17.3% for patients with hereditary disease. Hence, extra cau-
tion needs to be exercised in patients with retinoblas-
toma with hereditary mutation causing susceptibility to
fatal second cancers. Also, the age of the patient prior to
considering intra-arterial chemotherapy should be noted
because the irradiation susceptibility is higher in pa-
tients younger than 1 year.

Because intra-arterial chemotherapy is a relatively new
technique, the risks and adverse effects are still poorly
understood. With better understanding of the irradia-
tion damage during the procedure, the neurovascular in-
terventionists can modify the fluoroscopy time and dose
to minimize toxic effects.

In summary, fluoroscopy for catheter guidance is es-
ential for intra-arterial chemotherapy for retinoblas-
toma. However, concerns exist regarding irradiation toxic
effects from fluoroscopy in children. In this analysis, we
found that there was a measurable irradiation dose to the
lens in the affected eye. The latent period to develop cata-
ract can be very variable, and hence, long-term fol-
low-up is advisable. For patients who have received treat-
ments other than intra-arterial chemotherapy, the lens
could be more susceptible to irradiation damage and in-
crease their propensity to develop cataract. The irradia-
tion dose to other organs was lower than the level of toxic
effects. Nevertheless, reasonable caution is advised in the
use of fluoroscopy during intra-arterial chemotherapy.
Children with retinoblastoma are more susceptible to ir-
radiation-related second cancers and could be more prone
to malignancy with even low doses of irradiation. Long-
term close monitoring of these children is mandatory for
both ocular and systemic effects of irradiation and che-
motherapy.

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