Purpose: The main purpose of this study was to determine the efficacy of postenucleation adjuvant therapy in preventing metastasis in cases of high-risk retinoblastoma.

Methods: This was a retrospective, nonrandomized comparative study. Of 1020 consecutive patients with retinoblastoma who were managed at a referral center between January 1974 and December 1999, 80 (8%) of those analyzed had unilateral sporadic cases that were treated by primary enucleation and that had high-risk characteristics for metastasis on histopathology reports (anterior chamber seeding, iris infiltration, ciliary body infiltration, massive choroidal infiltration, invasion of optic nerve lamina cribrosa, retrolaminar optic nerve invasion, invasion of optic nerve transection, scleral infiltration, and extrascleral extension). The main outcome measure was the development of metastasis at a minimum follow-up period of 12 months.

Results: There were 44 male and 36 female patients, with age ranging from 1 day to 16 years (median, 33 months). A single histopathologic high-risk characteristic was present in 50 patients (62.5%). Thirty patients (37.5%) manifested 2 or more high-risk characteristics. Forty-six patients (58%) had received postenucleation adjuvant therapy (chemotherapy with or without orbital external beam radiotherapy). Adjuvant therapy was not administered in 34 patients (42%). Metastasis occurred in 10 patients (13%) at a median of 9 months (range, 6-57 months) following enucleation. Eight (80%) of those who developed metastasis had not received adjuvant therapy. A significant difference ($P = .02$) was found in the incidence of metastasis between the group that had received adjuvant therapy (4%; 2/46) and the group that had not (24%; 8/34). The beneficial effect of adjuvant therapy was statistically significant in subgroups of patients with massive choroidal infiltration ($P = .04$) or retrolaminar optic nerve invasion ($P = .04$). There were no adjuvant therapy–related serious systemic complications.

Conclusion: Postenucleation adjuvant therapy is safe and effective in significantly reducing the occurrence of metastasis in patients with retinoblastoma manifesting histopathologic high-risk characteristics.

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The prognosis of retinoblastoma has improved remarkably during the last century. It has evolved from an almost uniformly fatal malignant neoplasm to one that is cured in more than 90% of cases in medically advanced countries. The improved prognosis is believed to be due to earlier diagnosis and better methods of management. The major causes of mortality in patients with retinoblastoma include second malignant neoplasm, pinealoblastoma, and metastasis. Second malignant neoplasia and pinealoblastoma develop almost exclusively in heritable cases, whereas metastasis contributes significantly to tumor-related mortality in both heritable and nonheritable retinoblastoma. Metastatic retinoblastoma is reported to develop in less than 10% of patients in advanced countries. However, it is a major contributor to retinoblastoma-related mortality in developing nations. It may be possible to reduce the risk of metastatic retinoblastoma by providing postenucleation adjuvant therapy to selected patients. Adjuvant therapy may include systemic chemotherapy and orbital external beam radiotherapy.

With improved understanding of the risk factors predictive of metastasis and the availability of effective chemotherapy regimens for intraocular retinoblastoma, it would seem logical to consider adjuvant chemotherapy following enucleation to prevent metastasis in high-risk cases. Nevertheless, the utility of ad-
METHODS

This was a retrospective, nonrandomized study with a concurrent comparison group. The computerized patient database at the Oncology Service of Wills Eye Hospital (Philadelphia, Pa) was searched for patients with retinoblastoma. Of 1020 consecutive patients with retinoblastoma managed between January 1974 and December 1999, 630 had undergone enucleation. The medical records of those patients were reviewed for laterality of retinoblastoma, treatment modalities, and histopathologic features of the enucleated eye. Eighty patients (8%) with unilateral sporadic retinoblastoma who had undergone primary enucleation and had predefined specific high-risk characteristics on histopathology reports were identified for inclusion in this study (Table 1).

The patient data were reviewed for demographic information, clinical findings and management, and histopathologic features. The data collected included the date of diagnosis, age at diagnosis (months), sex (male, female), race (African American, white, Hispanic, Asian), hereditary pattern (familial, sporadic), laterality (unilateral, bilateral), the eye involved (right, left), and prior treatment or intraocular surgery. The clinical information included intraocular pressure, presence of macroscopic anterior chamber seeding, and neovascularization of the iris. Reese-Ellsworth staging of retinoblastoma was noted for each patient. Histopathology reports were reviewed for the presence of specific features (Table 1). Details of systemic evaluation (computed tomographic scan, magnetic resonance imaging, bone marrow examination, cerebrospinal fluid cytology) were recorded. Details of postenucleation adjuvant therapy (chemotherapy, orbital external beam radiotherapy) were noted. In patients who received adjuvant chemotherapy, the drug regimen, duration, and systemic complications (as periodically assessed by a pediatric oncologist) were noted. In those who received adjuvant orbital external beam radiotherapy, the total dose and fractionation schedule were recorded. If adjuvant therapy was not administered, the reason governing the decision was elicited. Information regarding the outcome included occurrence of metastasis, date of detection of metastasis, interval between enucleation and detection of metastasis (months), and the site of metastasis. The final patient outcome (alive without metastasis, alive with metastasis, alive with second malignant neoplasm, dead with metastasis, dead with second malignant neoplasm, or dead because of other causes), the date of last follow-up, and the duration of follow-up were noted.

The main interest of the statistical analysis was to assess the effect of adjuvant therapy in preventing metastasis. The comparison was between the group that received adjuvant therapy and the group that did not. In this nonrandomized retrospective study, we first tested for comparability of the 2 groups and the presence of potential confounding variables that interacted with adjuvant therapy. A t test was used for continuous variables and the Fisher exact test for discrete variables. We also tested the comparability of the 2 groups that received different chemotherapy regimens. The influence of adjuvant therapy in preventing metastasis in the presence of every individual (and various logical) combination of histopathologic risk factor was analyzed with the Fisher exact test. The proportion of patients free of metastasis was calculated using the Kaplan-Meier method. The date of enucleation was the starting point for the survival curve, and the detection of metastasis was the end point. The adjuvant therapy was examined for its relationship with the development of metastasis over time using the univariate Cox proportional hazards regression model.

RESULTS

Our series consisted of the cases of 80 patients with unilateral sporadic retinoblastomas who had undergone primary enucleation and had specific high-risk characteristics on histopathology report (Table 1). There were 44 male (55%) and 36 female (45%) patients, ranging in age from 1 day to 16 years (median, 33 months). Anterior chamber tumor seeding was clinically detectable in 17 eyes (21%), and neovascularization of iris was present in 30 eyes (38%). Retinoblastoma was clinically graded Reese-Ellsworth stage IVb in 1 eye (1%), Va in 18 eyes (23%), and Vb in 61 eyes (76%). The systemic examination, bone marrow biopsy, and cerebrospinal fluid cytology did not reveal the presence of metastasis in any of the patients at the time of initial diagnosis of retinoblastoma. All of the patients underwent enucleation 1 day to 2 weeks following the diagnosis of retinoblastoma. Fifty patients (62.5%) had a single histopathologic risk factor, while 30 (37.5%) had various combinations of multiple risk factors (2 risk factors in 20 patients, 3 risk factors in 9, and 5 risk factors in 1) (Figures 1, 2, 3, and 4). Table 2 summarizes the demographic, baseline clinical, and histopathologic features of the patients.

Adjuvant therapy was administered to 46 (58%) of 80 patients. The oncologist’s decision to withhold adjuvant therapy in 34 patients (42%) was based on the prevailing protocols (for 29 patients) or parental choice (for 5 patients). In the group that received adjuvant
therapy, each of the 46 patients received chemotherapy. The adjuvant chemotherapy regimen consisted of either a combination of vincristine sulfate, doxorubicin hydrochloride, and cyclophosphamide (prior to 1994), as in 21 patients (46%); or a combination of vincristine, etoposide, and carboplatin (from 1994 onwards), as in 25 patients (54%) (Table 3). The baseline characteristics of the groups that received 2 different chemotherapy regimens were comparable. The duration of chemotherapy ranged from 6 to 12 months (mean, 6.9±1.4 months). Except for episodes of reversible pancytopenia and infection in 11 patients (in 5 of 21 patients who received the vincristine-doxorubicin-cyclophosphamide combination and in 6 of 26 patients who received the vincristine-etoposide-carboplatin combination), there were no permanent systemic complications of chemotherapy. Twelve patients who had retrolaminar optic nerve invasion or invasion of optic nerve transection had additionally received intrathecal chemotherapy (methotrexate, 6-12 mg). Orbital external beam radiotherapy (4000-4500 rad [40-45 Gy]) was provided to 14 patients with invasion of optic nerve transection, scleral infiltration, or extrascleral extension. This was in addition to the chemo-

therapy that they all received. No form of adjuvant therapy was provided to 34 (42%) of 80 patients.

All of the patients were followed up for a minimum of 12 months after enucleation. The median duration of follow-up was 59 months (range, 12-287 months). None of the patients developed a second malignant neoplasm in our series. Systemic metastasis occurred in 10 patients (13%) at a median of 9 months (range, 6-57 months).
following the diagnosis of retinoblastoma. The sites of metastasis were the central nervous system in 3 patients, the skeletal system in 1 patient, and the combined skeletal and central nervous systems in 6 patients. Nine patients with metastasis died at a median of 15 months (range, 1-30 months) following the detection of metastasis, while 1 patient was alive in remission 16 months following detection of metastasis.

The rate of metastasis at the final follow-up visit was significantly lower (Fisher exact test, \( P = .02 \)) in the group that received adjuvant therapy (2/46, 4%) compared with the group that did not receive adjuvant therapy (8/34, 24%). Kaplan-Meier estimates showed that 96% of patients who received adjuvant therapy would remain free of metastasis at 10 years postenucleation compared with 76% of those who did not receive adjuvant therapy (Cox proportional hazards regression analysis, \( P = .03 \); relative risk, 0.175; 95% confidence interval, 0.037-0.824) (Figure 5).

Of the 2 patients who developed metastasis despite adjuvant therapy, 1 had retinoblastoma detected at birth, spontaneous corneal perforation, and 3 histopathologic high-risk characteristics (anterior chamber seeding, massive choroidal infiltration, and extrascleral extension). This patient received adjuvant chemotherapy and orbital external beam radiotherapy. The second patient had ciliary body infiltration and retrolaminar optic nerve invasion and received adjuvant chemotherapy. Metastasis was detected in these patients at 1 month and 2 months, respectively, following completion of chemotherapy. Of the 8 patients who developed metastasis in the group that did not receive adjuvant therapy, the histopathologic risk factors included anterior chamber seeding in 1 patient, retrolaminar optic nerve invasion in 3, a combination of anterior chamber seeding and massive choroidal infiltration in 1, massive choroidal infiltration and invasion of optic nerve lamina cribrosa in 1, massive choroidal infiltration and retrolaminar optic nerve invasion in 1, and massive choroidal infiltration and scleral infiltration in 1.

Many of the possible effects, including the difference in efficacy of 2 chemotherapy regimens and the additional role of intrathecal chemotherapy and orbital external beam radiotherapy, were statistically inestimable owing to the small number of events (metastasis) in the study. The influence of adjuvant therapy in preventing metastasis in each individual and the combination of histopathologic risk factors were analyzed by the Fisher exact test (Table 4). The beneficial effect of adjuvant therapy in preventing metastasis was statistically significant in patients with retrolaminar optic nerve invasion (\( P = .02 \)) as the single histopathologic risk factor, and with massive choroidal infiltration (\( P = .001 \)) as one of the multiple risk factors. Both these variables were again outstanding when all of the individual histopathologic risk factors were analyzed, irrespective of whether they existed in isolation or in combination (retrolaminar optic nerve invasion, \( P = .04 \); massive choroidal infiltration, \( P = .04 \)). Thirty-four patients had either retrolaminar optic nerve invasion or

![Figure 4](https://jamanetwork.com/)

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**Table 2. Demographic Characteristics, Clinical Features, and Histopathologic Factors in 80 Patients With High-Risk Characteristics of Retinoblastoma**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Entire Group (N = 80)</th>
<th>No Adjuvant Therapy (n = 34)</th>
<th>Adjuvant Therapy (n = 46)</th>
<th>( P ) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic and clinical features</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age, mo</td>
<td>33</td>
<td>30</td>
<td>34</td>
<td>.19</td>
</tr>
<tr>
<td>Mean intraocular pressure, mm Hg</td>
<td>25</td>
<td>28</td>
<td>23</td>
<td>.04</td>
</tr>
<tr>
<td>Neovascularization of iris</td>
<td>30</td>
<td>15</td>
<td>15</td>
<td>.35</td>
</tr>
<tr>
<td>Reese-Ellsworth grade V</td>
<td>79</td>
<td>34</td>
<td>45</td>
<td>. . .</td>
</tr>
<tr>
<td><strong>Histopathologic risk factors‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior chamber seeding</td>
<td>24</td>
<td>9</td>
<td>15</td>
<td>.63</td>
</tr>
<tr>
<td>Iris infiltration</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>.63</td>
</tr>
<tr>
<td>Ciliary body infiltration</td>
<td>10</td>
<td>3</td>
<td>7</td>
<td>.51</td>
</tr>
<tr>
<td>Massive choroidal infiltration</td>
<td>29</td>
<td>10</td>
<td>19</td>
<td>.35</td>
</tr>
<tr>
<td>Invasion of optic nerve lamina cribrosa</td>
<td>13</td>
<td>10</td>
<td>3</td>
<td>.01</td>
</tr>
<tr>
<td>Retrolaminar optic nerve invasion</td>
<td>29</td>
<td>10</td>
<td>19</td>
<td>.35</td>
</tr>
<tr>
<td>Invasion of optic nerve transaction</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>.07</td>
</tr>
<tr>
<td>Scleral infiltration</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>. . .</td>
</tr>
<tr>
<td>Extrascleral extension</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>.07</td>
</tr>
</tbody>
</table>

*All data are presented as number of patients. Ellipses indicate not applicable.

†\( P \) values are based on a comparison of the group that received adjuvant therapy with the group that did not receive adjuvant therapy by the Fisher exact test.

‡Fifty patients had a single risk factor, and 30 had multiple risk factors.
Etoposide was administered at 150 mg/m² on days 1 and 2 of each cycle. Carboplatin was administered at 560 mg/m² on day 1 of each cycle. Cyclophosphamide was administered at 300 mg/m² for 4 doses and 600 mg/m² for 8 doses at 21-day intervals.

Tocoagulation, laser thermotherapy, cryotherapy, and episcleral plaque brachytherapy are sources of subsequent systemic metastasis. Given the inability to detect micrometastases, it may be appropriate to consider adjuvant chemotherapy to eradicate micrometastatic disease. Notably, this strategy has been the basis of therapeutic success in the improvement of prognosis for other childhood neoplasia.

The identification of frequency and significance of histopathologic risk factors that reliably predict metastasis is vital for patient selection for adjuvant therapy. Several studies have addressed this issue. The reported occurrence of anterior chamber seeding (7%), massive choroidal infiltration (12%-23%), retrolaminar optic nerve invasion (6%-7%), retinal infiltration, ciliary body infiltration, and/or invasion of optic nerve lamina cribrosa as histopathologic risk factors. Twelve patients in this group did not receive adjuvant therapy, of whom 1 developed metastasis (P = .50).

The goals of management of retinoblastomas are, first, to save lives and, second, to salvage the eye and vision if possible. Therapy is individualized based on the overall clinical situation, including the risk for metastasis and second malignant neoplasm, systemic condition, laterality of the disease, size and location of the tumors, and visual prognosis. The available therapeutic options for retinoblastoma include enucleation, external beam radiotherapy, episcleral plaque brachytherapy, laser photoagulation, laser thermotherapy, chemotherapy, and orbital exenteration, either individually or in various combinations. Despite recent advances in retinoblastoma treatment and the current trend in favor of measures to salvage the eye and possibly vision, enucleation is still a valid primary therapeutic option for advanced unilateral retinoblastoma. Primary enucleation performed under such circumstances offers a high cure rate of 90% to 95%. Metastasis may still develop in 5% to 10% of patients undergoing primary enucleation for advanced unilateral retinoblastoma in developed countries, and at a much higher rate in developing nations.

It may be possible to prevent metastasis by identifying patients with risk factors predictive of metastasis and providing them with adjuvant therapy. It seems reasonable to assume that micrometastases present at the time of enucleation and residual orbital disease are the sources of subsequent systemic metastasis. Given the inability to detect micrometastases, it may be appropriate to consider adjuvant chemotherapy to eradicate micrometastatic disease. Notably, this strategy has been the basis of therapeutic success in the improvement of prognosis for other childhood neoplasia.

The chemotherapy regimens used in 46 patients of retinoblastoma with high-risk characteristics are shown in Table 3.

### Table 3. Chemotherapy Regimens in 46 Patients of Retinoblastoma With High-Risk Characteristics

<table>
<thead>
<tr>
<th>Chemotherapy Regimen</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine sulfate + doxorubicin†</td>
<td>21</td>
</tr>
<tr>
<td>Vincristine + etoposide + carboplatin†</td>
<td>25</td>
</tr>
</tbody>
</table>

*Vincristine sulfate was administered at 1.5 mg/m² for 12 doses, 6 times weekly, then at 21-day intervals. Doxorubicin hydrochloride was administered at 60 mg/m² for 4 doses at 21-day intervals. Cyclophosphamide was administered at 300 mg/m² for 4 doses and 600 mg/m² for 8 doses at 21-day intervals.

†Vincristine sulfate was administered at 1.5 mg/m² on day 1 of each cycle. Carboplatin was administered at 560 mg/m² on day 1 of each cycle. Etoposide was administered at 150 mg/m² on days 1 and 2 of each cycle (6 cycles given at 28-day intervals).

The identification of frequency and significance of histopathologic risk factors that reliably predict metastasis is vital for patient selection for adjuvant therapy. Several studies have addressed this issue. The reported occurrence of anterior chamber seeding (7%), massive choroidal infiltration (12%-23%), inv.

The identification of frequency and significance of histopathologic risk factors that reliably predict metastasis is vital for patient selection for adjuvant therapy. Several studies have addressed this issue. The reported occurrence of anterior chamber seeding (7%), massive choroidal infiltration (12%-23%), retrolaminar optic nerve invasion (6%-7%), and extrascleral extension (2%-13%) varies widely even in developed countries. Velmuganti et al reported 21% of the 76 eyes enucleated for advanced retinoblastoma in India had anterior chamber seeding, while 54% had massive choroidal infiltration, 36% had optic nerve invasion at or beyond the optic nerve lamina cribrosa, and 7% had scleral infiltration or extrascleral extension. This is strikingly higher compared with the data from developed countries. It is now generally agreed that massive choroidal infiltra-

**Comment**

Figure 5. Kaplan-Meier estimates of the proportion of patients free of metastasis in the group that received adjuvant therapy (triangle line) and the group that did not (open circle line).

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Table 4. Presence of High-Risk Characteristics on Histopathology and Incidence of Metastasis in 80 Patients With Retinoblastoma

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Adjuvant Therapy</th>
<th>No Adjuvant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Metastasis Present</td>
<td>Metastasis Absent</td>
</tr>
<tr>
<td>Single risk factor (n = 50)</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Anterior chamber seeding (n = 11)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Ciliary body infiltration (n = 1)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Massive choroidal infiltration (n = 8)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Invasion of optic nerve lamina cribrosa (n = 10)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Retrolaminar optic nerve invasion (n = 19)</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Invasion of optic nerve transection (n = 1)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Multiple risk factors (n = 30)</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Anterior chamber seeding (n = 13)</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Iris infiltration (n = 4)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Ciliary body infiltration (n = 9)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Massive choroidal infiltration (n = 21)</td>
<td>1</td>
<td>16</td>
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<td>Invasion of optic nerve lamina cribrosa (n = 3)</td>
<td>0</td>
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<tr>
<td>Retrolaminar optic nerve invasion (n = 10)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Invasion of optic nerve transection (n = 4)</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Scleral infiltration (n = 3)</td>
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</tr>
<tr>
<td>Extraciliary extension (n = 5)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>All risk factors (n = 80)†</td>
<td>2</td>
<td>44</td>
</tr>
<tr>
<td>Anterior chamber seeding (n = 24)</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Iris infiltration (n = 4)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Ciliary body infiltration (n = 10)</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Massive choroidal infiltration (n = 29)</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Invasion of optic nerve lamina cribrosa (n = 13)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Retrolaminar optic nerve invasion (n = 29)</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Invasion of optic nerve transection (n = 5)</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Scleral infiltration (n = 3)</td>
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</tr>
<tr>
<td>Extraciliary extension (n = 5)</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

*All data are presented as number of patients. P values were determined by Fisher exact test.
†Risk factors include all individual risk factors.

Adjuvant therapy, retrolaminar optic nerve invasion, invasion of the optic nerve to transection, scleral infiltration, and extrascleral extension are risk factors predictive of metastasis. However, the role and significance of anterior chamber seeding, iris infiltration, ciliary body infiltration, and invasion of the optic nerve lamina cribrosa as risk factors for metastatic retinoblastoma remain debatable.

Studies initiated in the 1970s on adjuvant therapy to minimize the risk of metastasis were marked by variable results and provided no firm recommendation. In a prospective randomized study by the Children’s Cancer Study Group, comprising 14 patients with high-risk retinoblastoma treated with adjuvant chemotherapy, no significant difference in survival was demonstrated in comparison with the control group. A prospective study by Zelter et al also showed equivocal results. Recently, Mustafa et al observed that despite postenucleation and adjuvant chemotherapy with vincristine, doxorubicin, and cyclophosphamide, patients with retinoblastoma having retrolaminar optic nerve invasion had a low survival rate. Chantada et al, based on their study of patients with risk factors, stated that adjuvant chemotherapy was not warranted in patients with prelaminar optic nerve invasion and probably not in cases with retrolaminar optic nerve invasion and isolated choroidal infiltration. On the contrary, several studies have indicated that adjuvant chemotherapy was beneficial. Howarth et al, in a small prospective series of 14 patients, found a beneficial role of adjuvant chemotherapy for high-risk retinoblastoma. Keith found benefit with adjuvant chemotherapy in these patients, but issued a warning regarding the possibility of chemotherapy-induced second malignant neoplasms. Hungerford commented that all children in London, England, with massive choroidal infiltration or retrolaminar optic nerve invasion had received systemic adjuvant chemotherapy since 1985, and none of them had developed metastasis. Kheifaiou et al found a statistically significant decrease in retinoblastoma metastasis in a diverse group of 75 patients treated with adjuvant chemotherapy. In a prospective evaluation by Schwartzman et al of a stage-based (Grabowski and Abramson) protocol, it was found that adjuvant chemotherapy was beneficial in cases with extraciliary extension of retinoblastoma. An approach of high-dose chemotherapy followed by hematopoietic stem cell rescue was beneficial in a diverse group of patients with high-risk retinoblastoma, but results were comparable to those of conventional, less aggressive protocols. Uusitalo et al concluded that chemoprophylaxis is necessary for patients with tumor invasion of optic nerve transection and is likely to be beneficial in preventing metastasis in patients with retrolaminar optic nerve invasion.

On reviewing the published literature regarding the role of adjuvant therapy in high-risk retinoblas-
et al35 have reported the beneficial effect of adjuvant or-
gery in an eye with unsuspected retinoblastoma) may also
crscopic extraocular tumor cell seeding (scleral infil-
stantly, the absence of a control group (metastasis),21,25,28,33,39 the lack of comparable stratifica-
ument for subgroup analysis,21,23,25,26,28,31-34and more signifi-
remained significantly in the subgroup having any degree of
clusion criteria. The adjuvant treatment was mainly de-
histopathologic high-risk characteristics as defined by our
sistance significant in the subgroup having any degree of
a number of patients and overall results in some of the studies may be different from the data compiled in the table because only relevant and comparable
table for subgroup analysis,21,23,25,26,28,31-34 and more signifi-
ment criteria. The adjuvant treatment was mainly de-
trolled trial dealing with the issue of adjuvant therapy.
relating factors.22-34,39 The absence of strict inclusion criteria, the inclusion of
placement, multiple prior therapy in cases with second-
induced confounding variables, making it difficult to objectively interpret the results of these
of massive choroidal infiltration or retrolamina.
extraocular extension: RE, Reese-Ellsworth; AC, anterior chamber seeding; CB, ciliary body infiltration; ON-L, invasion of optic nerve lamina cribrosa; SCL, scleral
infiltration; V, vincristine sulfate; C, cyclophosphamide; D, doxorubicin hydrochloride; Cp, carbonplatin; and E, etoposide. Treated cases represented here are those
in the patient received adjuvant chemotherapy.
and extracranial metastasis from retinoblastoma, metastasis,21-34 are different from the data compiled in the table because only relevant and comparable
tions were to eliminate the influence of confounding factors
the presence of massive choroidal infiltration or retro-
tinoblastoma. However, to our knowl-
edge, there are no studies that have evaluated the role of
extremetoma.21-34,39 The presence of histopathologically proven resi-
section and extraocular extension) may warrant the use of
kay external beam radiotherapy.4 In addition, clinical
nuclear tumor cell seeding (scleral infiltration by the tumor, spontaneous or accidental perforation of an eye with retinoblastoma, intraocular surgery in an eye with unsuspected retinoblastoma) may also warrant using orbital external beam radiotherapy.35 Shields
have reported the beneficial effect of adjuvant orbital
extraocular beam radiotherapy used in addition to sys-
tic chemotherapy in preventing metastasis in a group of
children who had undergone intraocular surgery for
unsuspected retinoblastoma. However, to our knowl-
edge, there are no studies that have evaluated the role of
adjuvant orbital external beam radiotherapy in prevent-
ing metastasis in patients with histopathologically proven
residual orbital retinoblastoma.
In the absence of a randomized prospective con-
trolled trial dealing with the issue of adjuvant therapy, we believe that our large study with a long-term
follow-up (median, 59 months) provides useful infor-
mation. One major drawback of our study was that it
was retrospective in nature and was nonrandomized. We, however, had a concurrent control group of
patients (Table 2) who met all the inclusion criteria but
who did not receive adjuvant therapy. We used specific
predetermined histopathologic characteristics for inclu-
sion of patients into this study (Table 1). Our series
consisted only of patients with unilateral sporadic reti-
oblastoma who underwent primary enucleation. This
was to eliminate the influence of confounding factors
such as tumor in the nonenucleated eye in bilateral
cases, and multiple prior therapy in cases with second-
ary enucleation on the end point. However, our strict
selection criteria may have resulted in understimation of
the incidence of metastasis. A minimum follow-up of
1 year was established to allow inclusion of metastatic
events that generally occur at a mean of 9 months fol-
lowing enucleation.6
We found that administration of adjuvant therapy
significantly reduced the risk of metastasis in patients with
histopathologic high-risk characteristics as defined by our
inclusion criteria. The adjuvant treatment was mainly de-
termined by the prevailing protocol of the treating on-
cologist. The group that received adjuvant therapy was
(understandably) selected for having a comparatively
higher risk of metastasis than the group that did not re-
ceive adjuvant therapy (Table 2). Therefore, it seems that
adjuvant therapy resulted in a significant reduction in the
incidence of metastasis that was below that of the rela-
tively low-risk group that was not provided adjuvant
therapy.
It is possible that not all the histopathologic factors
are equivalent in their risk for metastasis. The statistical
analysis was limited by the small number of patients and
the infrequent number of events (metastasis) in each
subgroup. The beneficial effect of adjuvant therapy in
preventing metastasis was statistically significant in the
presence of massive choroidal infiltration or retro-
laminar optic nerve invasion. The benefit was also statisti-
cally significant in the subgroup having any degree of
optic nerve invasion beyond the lamina cribrosa (retro-
laminar optic nerve invasion and invasion of optic
nerve transection). We were unable to analyze the ben-
efficial effect of adjuvant therapy on individuals in

Table 5. The Role of Adjuvant Chemotherapy in Preventing Metastasis in
High-Risk Retinoblastoma: Survey of the Published Literature*

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Study Design</th>
<th>Control Group</th>
<th>Selection Criteria</th>
<th>No. (%) of Metastases</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howarth et al21 (1980)</td>
<td>Prospective</td>
<td>No</td>
<td>CHR, ON-RL, ON-TS, ESE</td>
<td>14</td>
<td>V, C (7)</td>
</tr>
<tr>
<td>Keith23 (1989)</td>
<td>Retrospective</td>
<td>No</td>
<td>ON-RL, ON-TS, ESE</td>
<td>26</td>
<td>V, C (4)</td>
</tr>
<tr>
<td>Zelter et al24 (1991)</td>
<td>Retrospective</td>
<td>No</td>
<td>CHR, ON-RL, ON-TS, ESE</td>
<td>24</td>
<td>V, D, C (33)</td>
</tr>
<tr>
<td>Hungerford25 (1993)</td>
<td>Retrospective</td>
<td>No</td>
<td>CHR, ON-RL</td>
<td>11</td>
<td>NA (0)</td>
</tr>
<tr>
<td>Khelfaoui et al26 (1996)</td>
<td>Retrospective</td>
<td>Yes</td>
<td>Variable</td>
<td>75</td>
<td>Variable (6)</td>
</tr>
<tr>
<td>Schwartzman et al27 (1996)</td>
<td>Prospective</td>
<td>No</td>
<td>ON-RL, ON-TS, ESE</td>
<td>29</td>
<td>V, D, C (14)</td>
</tr>
<tr>
<td>Mustafa et al29 (1999)</td>
<td>Retrospective</td>
<td>No</td>
<td>CHR, ON-RL, ON-TS, ESE</td>
<td>27</td>
<td>V, D, C (19)</td>
</tr>
<tr>
<td>Uusitalo et al30 (2001)</td>
<td>Retrospective</td>
<td>Yes</td>
<td>ON-RL, ON-TS</td>
<td>11</td>
<td>Variable (9)</td>
</tr>
<tr>
<td>Current study (2001)</td>
<td>Retrospective</td>
<td>Yes</td>
<td>AC, CB, CHR, ON-L, ON-RL, ON-TS, SCL, ESE</td>
<td>46</td>
<td>V, D, C or V, Cp, E (2)</td>
</tr>
</tbody>
</table>

*The number of patients and overall results in some of the studies may be different from the data compiled in the table because only relevant and comparable
data are tabulated. CHR indicates massive choroidal infiltration; ON-RL, retrolaminar optic nerve invasion; ON-TS, invasion of optic nerve transection; ESE, extraocular infiltration; RE, Reese-Ellsworth; AC, anterior chamber seeding; CB, ciliary body infiltration; ON-L, invasion of optic nerve lamina cribrosa; SCL, scleral infiltration; V, vincristine sulfate; C, cyclophosphamide; D, doxorubicin hydrochloride; Cp, carbonplatin; and E, etoposide. Treated cases represented here are those
in which the patient received adjuvant chemotherapy.

†Study was also randomized.

The presence of histopathologically proven resi-
by orbital external beam radiotherapy. In addition, clinical
circumstances that possibly increase the risk of mi-
roscopic extraocular tumor cell seeding (scleral infil-
tration by the tumor, spontaneous or accidental perfor-
ation of an eye with retinoblastoma, intraocular sur-
ery in an eye with unsuspected retinoblastoma) may also
warrant using orbital external beam radiotherapy.35 Shields
et al35 have reported the beneficial effect of adjuvant orbital
external beam radiotherapy used in addition to sys-
temic chemotherapy in preventing metastasis in a group of
children who had undergone intraocular surgery for
unsuspected retinoblastoma. However, to our knowl-
edge, there are no studies that have evaluated the role of
adjuvant orbital external beam radiotherapy in prevent-
ing metastasis in patients with histopathologically proven
residual orbital retinoblastoma.
In the absence of a randomized prospective con-
trolled trial dealing with the issue of adjuvant therapy, we believe that our large study with a long-term
follow-up (median, 59 months) provides useful infor-
mation. One major drawback of our study was that it
was retrospective in nature and was nonrandomized. We, however, had a concurrent control group of
patients (Table 2) who met all the inclusion criteria but
who did not receive adjuvant therapy. We used specific
predetermined histopathologic characteristics for inclu-
sion of patients into this study (Table 1). Our series
consisted only of patients with unilateral sporadic reti-
oblastoma who underwent primary enucleation. This
was to eliminate the influence of confounding factors
such as tumor in the nonenucleated eye in bilateral
cases, and multiple prior therapy in cases with second-
ary enucleation on the end point. However, our strict
selection criteria may have resulted in understimation of
the incidence of metastasis. A minimum follow-up of
1 year was established to allow inclusion of metastatic
events that generally occur at a mean of 9 months fol-
lowing enucleation.6
We found that administration of adjuvant therapy
significantly reduced the risk of metastasis in patients with
histopathologic high-risk characteristics as defined by our
inclusion criteria. The adjuvant treatment was mainly de-
termined by the prevailing protocol of the treating on-
cologist. The group that received adjuvant therapy was
(understandably) selected for having a comparatively
higher risk of metastasis than the group that did not re-
ceive adjuvant therapy (Table 2). Therefore, it seems that
adjuvant therapy resulted in a significant reduction in the
incidence of metastasis that was below that of the rela-
tively low-risk group that was not provided adjuvant
therapy.
It is possible that not all the histopathologic factors
are equivalent in their risk for metastasis. The statistical
analysis was limited by the small number of patients and
the infrequent number of events (metastasis) in each
subgroup. The beneficial effect of adjuvant therapy in
preventing metastasis was statistically significant in the
presence of massive choroidal infiltration or retro-
laminar optic nerve invasion. The benefit was also statisti-
cally significant in the subgroup having any degree of
optic nerve invasion beyond the lamina cribrosa (retro-
laminar optic nerve invasion and invasion of optic
nerve transection). We were unable to analyze the ben-
efficial effect of adjuvant therapy on individuals in
groups with invasion of optic nerve transection and extrascleral extension because all of the patients with these risk factors had been provided with adjuvant therapy. We found that the adjuvant therapy was most beneficial when massive choroidal infiltration, retrolaminar optic nerve invasion, invasion of optic nerve transection, scleral infiltration, and/or extrascleral extension were present. It is, however, difficult to completely negate the role of the other histopathologic factors, such as anterior chamber seeding, iris infiltration, ciliary body infiltration, and invasion of optic nerve lamina cribrosa in causing metastasis.

Various combinations of chemotherapeutic drugs have been used in the past (Table 5). Throughout the years, we have used a combination of vincristine, doxorubicin, and cyclophosphamide or a combination of vincristine, carboplatin, and etoposide (Table 3). The baseline characteristics of the groups that received 2 chemotherapy regimens were comparable. The difference in the beneficial effects of the 2 drug regimens could not be evaluated because of the small number of patients who developed metastasis. Questions regarding the safety of chemotherapy involved systemic toxic effects and possible increased risk of second malignant neoplasms with cytotoxic therapy. None of the patients in our series suffered irreversible systemic toxic effects with either of the drug regimens. There was no second malignant neoplasm observed in our series, which comprised cases of unilateral retinoblastomas at a median follow-up of 59 months. The question regarding possible induction of second malignant neoplasms in a susceptible patient population could be answered only by large controlled long-term studies. Based on our results, we cannot comment on the ideal drug regimen for adjuvant therapy. A combination of vincristine, doxorubicin, and cyclophosphamide has the advantage of being relatively less expensive, and potentially has fewer severe systemic adverse effects. However, carboplatin has high penetration into the central nervous system and bone marrow, which are the 2 potential sites of metastasis. Combining carboplatin with etoposide is synergistic when used for embryonal neuroectodermal tumors in children.

Some of the patients who received adjuvant chemotherapy additionally received orbital external beam radiotherapy. It is difficult to analyze and comment on the individual role of adjuvant chemotherapy and adjuvant orbital external beam radiotherapy in preventing systemic metastasis. Each modality may have potentiated the beneficial effect of the other in preventing systemic metastases.

Our current practice is to administer 6 cycles of a combination of carboplatin, etoposide, and vincristine (identical to the protocol used for chemoreduction of intraocular retinoblastoma) in patients with histopathologic risk factors for metastasis (Table 1). We currently do not use adjuvant intrathecal methotrexate. All patients with invasion of optic nerve transection, scleral infiltration, and extrascleral extension currently receive adjuvant orbital external beam radiotherapy.

In summary, we found that adjuvant therapy was effective in significantly reducing the risk of metastasis in high-risk cases of retinoblastoma. The incidence of metastasis was 4% in those who received adjuvant therapy, compared with 24% in those who did not. Based on the results of our study, it is reasonable to conclude that adjuvant therapy is beneficial in reducing the risk of metastasis in cases of retinoblastoma with high-risk characteristics on histopathology reports. The beneficial effect of adjuvant therapy seems pronounced in the subgroup of patients with massive choroidal infiltration and retrolaminar optic nerve invasion. A large randomized multicentric prospective study may help in resolving some of the outstanding issues that include stratification of risk factors and identification of a specific subset of high-risk characteristics in the presence of which postenucleation adjuvant therapy may be most beneficial.

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REFERENCES


