Retinoblastoma in the 20th Century: Past Success and Future Challenges
The Weisenfeld Lecture

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Retinoblastoma is the most common primary cancer of the eye in children. Although it represents only approximately 4% of childhood cancer and less than 1% of all human cancers, it is of widespread interest because it was the first cancer gene identified and cloned (in 1986). More than 70 years ago, it was recognized that retinoblastoma sometimes has a genetic basis and that the pattern (when genetic) is classic Mendelian autosomal dominant. It was not until Alfred Knudson proposed his two-hit hypothesis and the subsequent molecular confirmation of his calculation that it was recognized that this autosomal-dominant pattern is caused by the loss of a normally occurring gene that is now referred to as the RB1 gene. Although it was originally thought to be of importance only in retinal cancers, it is now recognized that loss of the normal RB1 gene is an important step in cancer development in most adult nonocular cancers.

In the United States there are approximately 350 newly diagnosed cases of retinoblastoma yearly, and worldwide estimates are 5000 to 8000 cases each year. When compared to adult lung cancer with almost 300,000 cases yearly, retinoblastoma is so obscure that little definitive scientific information is known about this rare cancer. How could clinicians at the turn of the 19th century ever come to understand this cancer well enough to diagnose it accurately and treat it? How could such a rare cancer ever have enough tissue to study or even be diagnosed accurately without biopsy? How could studies be designed to establish effective treatments? Imagine yourself attempting to manage retinoblastoma in the 19th century with only the candle direct ophthalmoscope, no anesthesia, and no devices designed to establish effective treatments? Imagine yourself attempting to manage retinoblastoma in the 19th century with only the candle direct ophthalmoscope, no anesthesia, and nothing published on this rare disease.

But although it seemed an impossible task to treat this disease 100 years ago, in 2004 there will be almost 1000 publications on retinoblastoma worldwide, 99% of children in the Western world will survive this cancer, and 90% will retain normal vision in one eye. How this came about and the unexpected and challenging “complication” of this success will be the subject of this review. An excellent comprehensive review of the history of retinoblastoma has been published by Albert.

History

Although widely reported to be first recognized by the Dutch physician Petrus Pauwius in 1597, sculpture found in Peru suggests documentation of the disease 2000 years ago. The first enucleation for retinoblastoma was advocated by James Wadrop in 1809, and the first cases in the United States were reported from New York Hospital in the later 1800s. By 1869 there were reports of survivors of retinoblastoma, and Hirschberg had a 5% survival rate. By 1897, 17% of children survived (enucleation and exenteration were the only treatments available). However, as late as 1905 it was stated that “there is no case on record of a child from whom a gliomatous (retinoblastoma) eye has been removed, growing up and having children with glioma (retinoblastoma).”

The first description of an eye that was successfully treated with radiation for retinoblastoma was published in 1903 when a Texas physician reported success (defined as a child, not the eye, surviving treatment). Modest improvements in survival occurred over the next 20 years. Interestingly, retinoblastoma became a cancer managed by ophthalmologists, not pediatricians and, even in later years, not by pediatric oncologists. In fact, retinoblastoma is the only pediatric cancer managed by ophthalmologists. It is even more striking when you realize that, in 2003, it is the pediatric cancer with the highest survival rate.

Treatments and Classification

The success in managing retinoblastoma is attributable to general developments in medicine, along with the specialized development of what were thought to be purely ophthalmic techniques (such as laser photocoagulation and cryosurgery). In 1921 the first eye with retinoblastoma was salvaged and in 1926 the first case was reported of successful treatment of retinoblastoma with retention of sight.

It was in the 1930s that retinoblastoma attracted some very talented clinicians who spearheaded the development of better techniques for diagnosis and treatment. By this time, anesthesia techniques allowed the clinicians more time and greater ease in the examination of children, and newer eye drop preparations allowed more certain pupillary dilation in a timely fashion.

In the United States, Algeron Reese with his colleagues developed techniques for radiation and identified patterns of progression after external beam radiation. Although success with externally applied radiation was obvious to these investigators, local ophthalmic complications were frequent. They then began working with radiologists (who were to become radiation oncologists) and realized that by altering a few parameters they saved more eyes with useful vision. They progressively lowered the dose from more than 20,000 rads (now cGy) to the present-day 3500 to 4500 cGy. They began using radiation sources with characteristics that allowed the dose to the eye to be higher than that to the bone (earlier, lower-voltage machines delivered a higher dose to the bone when treating an eye); they learned to avoid the anterior segment by delivering radiation from the side of the head (“lateral portal”); and they learned that, by delivering the same total dose over more days (fractionation), they had as many cures with higher ocular salvage rates.
Meanwhile in England, Henry Stallard\(^7\), too, was exploring radiation therapy and discovering exactly the same treatment parameters. Stimulated by a case reported by Foster Moore, Stallard realized that there might be a way he could bring the source of radiation directly to the eye and avoid many of the complications of external beam radiation. His cobalt plaques were the beginnings of modern-day brachytherapy; and, though he began working with them in the 1930s, it was not until 1969 that the first plaques were introduced in the United States.

In the late 1950s, two additional important developments occurred. In the United States, Robert Ellsworth, working with Reese, developed a classification scheme for retinoblastoma. This was not a true staging system, but it allowed investigators throughout the world to compare results among different techniques and emphasized that failures of lateral portal radiation were due to larger-sized tumors, more anteriorly located tumors, and tumors with vitreous seeds.

The earliest attempt at focally treating retinoblastoma was the use of diathermy. In the early 1930s Weve\(^8\) introduced this technique to ophthalmology with some good results. When diathermy was applied across the sclera, a chorioretinal scar developed that sometimes cured the retinoblastoma and allowed retention of the eye. Unfortunately electric current is carried by blood vessels, and scarring was often more extensive than desired. In addition, scleral thinning helped promote extraocular disease; and, though some patients survived with good vision, most had complications that led to abandoning the technique. The experience with diathermy did, however, spark the idea that intraocular foci of retinoblastoma could be successfully treated focally with photocoagulation. The technique was first used to treat macular holes, Meyer-Schwickerath quickly recognized that it could be successfully used for intraocular retinoblastoma, and results of the technique began appearing in 1959.

At about the same time, the indirect ophthalmoscope, introduced in the United States by Charles Schepens in the late 1940s, began to be used more widely, and, for the first time, clinicians could reliably examine the peripheral retina.

Cryotherapy was introduced by Harvey Lincoff et al.\(^9\) in the 1960s and has proven to be an important adjunct in the treatment of peripheral, small retinoblastomas without compromising visual function.

Diagnostic imaging improved in ophthalmology during the 1960s, 1970s, and 1980s. Ophthalmic ultrasound allowed clinicians to diagnose intraocular tumors accurately and the development of computed tomography (CT) and then magnetic resonance imaging (MRI) techniques further increased accuracy in diagnosis. One hundred years ago, most eyes enucleated for retinoblastoma were found to have something else. In a 1974 review from the Armed Forces Institute of Pathology,\(^10\) 24% of enucleated eyes had been misdiagnosed. However, because of improved diagnostic techniques, there has not been an eye incorrectly enucleated for suspected retinoblastoma in 30 years at the Memorial-Sloan Kettering Cancer Center in New York.

Chemotherapy was first introduced for retinoblastoma in 1953 when Carl Kupfer\(^11\) used systemically administered nitrogen mustard. Although many people assume that the first use of systemic chemotherapy was for extraocular disease, in reality it was Kupfer’s idea that, with the use of chemotherapy, the total radiation dose needed for the treatment of intraocular retinoblastoma could be diminished. It was not known at that time that the dose of radiation could have been diminished without compromising success, but when Reese examined Kupfer’s patient, he was so impressed that he immediately began using systemic chemotherapy (triethylenemelamine) and decreasing the dose of radiation. Hundreds of patients were so treated in New York, but ultimately the technique was abandoned\(^12\) because of immediate side effects (including death) and the eventual recognition that the dose of externally administered radiotherapy could be safely and effectively diminished without the use of chemotherapy.

We became interested in systemic chemotherapy for intraocular disease again in the 1970s. This time we used drugs that had been shown to have an effect on metastatic retinoblastoma: vincristine, cyclophosphamide, and doxorubicin. We quickly discovered that even though there was a dramatic response to systemically administered chemotherapy, the tumors regrew after treatment was stopped. Once that was recognized, we began using systemic chemotherapy simply to shrink tumors, which we then treated focally with photocoagulation, cryotherapy, or brachytherapy (with cobalt plaques).

In 1982 the American Cancer Society used one of our fundus photographs of a chemotherapy-treated eye on the cover of one of their issues of CA, A Cancer Journal for Clinicians.\(^13\)

In the 1990s, clinicians throughout the world, following the lead of the Los Angeles group in the United States and the London group in England, began using systemic chemotherapy for treatment of intraocular disease. Detailed analysis of these many and ongoing papers is presented elsewhere.\(^14\) Systemic chemotherapy is presently the most common technique used in eyes with bilateral retinoblastoma and select cases of unilateral retinoblastoma. For tumors classified as Reese-Ellsworth groups I, II, or III, the idea is to shrink the tumor (chemoreduction) and then treat focally. For advanced group IV and V tumors it is used in the hope of avoiding enucleation or external beam radiation.

In an attempt to avoid the systemic toxicity of chemotherapy, work began in Miami\(^15\) and New York\(^16\) on the potential use of locally administered chemotherapy for intraocular disease. We treated the first patients, and since then local chemotherapy has been used successfully worldwide. Although we have cures cases involving vitreous seeds with repeated local chemotherapy alone, most cases ultimately relapse unless the site of origin of the vitreous seeds is also identified and successfully treated.

Meanwhile, progress has been made in the treatment of metastatic retinoblastoma. Just as there was a need for a classification (not staging) system for intraocular disease in the 1950s, there was a similar need in the latter part of the 20th century, as treatment approaches were being refined. An excellent scheme was proposed from St. Jude’s Children’s Research Hospital in Memphis, but the most widely used system is the one that we developed in New York.\(^17\):

The Grabowski-Abramson Classification Scheme for Intraocular Retinoblastoma

I. Intraocular disease
   a. Retinal tumor
   b. Extension into choroid
   c. Extension up to lamina cribrosa
   d. Extension into sclera

II. Orbital disease
   a. Orbital tumor
      1. Suspicious (pathology of scattered episcleral tumor cells)
      2. Proven (biopsy-proven orbital tumor)
   b. Positive regional node

III. Optic nerve disease
   a. Tumor beyond lamina but not up to cut section
   b. Tumor at cut section of optic nerve
IV. Intracranial metastasis
   a. Positive cerebrospinal fluid only
   b. Retinoblastoma mass in brain
V. Hematogenous metastasis
   a. Positive marrow/bone lesions
   b. Other organ involvement

Work in New York, Latin America, and Paris has demonstrated that metastatic retinoblastoma is curable with multimodal chemotherapy (including bone marrow transplant) and radiation. Over 25 years, patients who had orbital recurrence went from a 10% cure rate to a 90% cure rate, and metastatic disease, universally fatal 50 years ago, is now being cured more than 75% of the time. Subsequent systemic metastases rarely develop in children who remain disease free after 5 years (<1% of the time).

It is striking that all this was accomplished without collaborative trials, without central registration of patients, and without randomized studies. In that sense, ophthalmic oncology has not followed the modern model of cancer investigation. One would expect that little could be learned about such a rare cancer, but in fact the improvement in survival of retinoblastoma has been faster than that of any other cancer in children or adults. This was possible because of keen insights by a few talented clinicians and the fact that the new treatments were so obviously successful that clinical trials were not necessary. When photocoagulation, cryotherapy, and plaques began saving most eyes that were previously untreatable, there was no need for controlled trials. Only one prospective multicenter randomized trial for retinoblastoma has ever been conducted. That protocol was the Children’s Cancer Study Group (CSG) 961 protocol. The study (which was never published), with just over 100 patients (>90% from the New York Center), looked at the impact of adjuvant chemotherapy (vincristine and cyclophosphamide) after enucleation versus enucleation alone for unilateral, enucleated retinoblastoma without optic nerve extension. Interestingly, only two patients in the series died and both had received chemotherapy. The two conclusions of the study were that there is no benefit of adjuvant chemotherapy in patients who undergo unilateral enucleation without optic nerve disease and that systemically administered vincristine and cyclophosphamide were insufficient to prevent metastatic disease in patients who had optic nerve extension. It was in 1949 that Reese published his landmark paper demonstrating that bilateral retinoblastoma could be successfully managed by enucleating the more-involved eye and irradiating the less-involved eye. This report in 1949 of 15-year results with bilateral retinoblastoma was a major work that influenced all future retinoblastoma management worldwide. In that report, tucked away in the latter pages, was an observation that in 2 of the 55 patients described, additional cancers developed that were not in the eye. Both of these were sarcomas, and in both cases the patients died as a result of the sarcoma and not of the retinoblastoma itself. Although these two cases have usually been thought to be the first reported examples of second cancers, Schoenberg described a 2-year-old child who was treated with radium and 30 years later had a "scar tissue sarcoma" develop in the irradiated temporal bone. That patient later died of metastases.

SECOND CANCERS

In 1961, Forrest reported 21 cases of tumors that developed in ophthalmic patients who had received therapeutic radiation for ocular or orbital malignancies. He was struck that in 17 of his 21 cases the original tumor had been retinoblastoma. He defined these as "radiation-induced," which was then defined as tumors that appeared after high doses of radiation, after a long latent period, and in the irradiated area. Although there was truth in each of these observations, we now know that the assumptions about each of these three premises were incorrect.

For the next 15 years many papers appeared correlating exposure to radiation in patients who had subsequent cancers. When I reviewed the world literature in 1974, I realized that there were more reports on this phenomenon than patients reported, and thought that there might be more to this story.

Our work and, in parallel, the work performed in Holland and England, have allowed us to understand many, but not all aspects of subsequent cancer development in retinoblastoma survivors. These cancers have universally been called "second nonocular cancers," a term I coined, to emphasize that the cancers are the second cancer (retinoblastoma being the first cancer) in these patients and that the second cancers were not oculor but outside the eye. In reality, however, these cancers are usually the second cancer but the first nonocular cancer to develop. Since the term I adopted 30 years ago is in widespread use, I will continue to use it here.

In the 1970s, I reviewed 1093 retinoblastoma cases treated in New York and combined them with 1214 cases on file at the Armed Forces Institute of Pathology and made some important observations, which are listed below:

1. Although the majority of the retinoblastoma cases were unilateral, 98% of the patients in whom second cancers developed had been treated for bilateral retinoblastoma. This suggested a gene effect, but at the time the genetics of retinoblastoma were not clear, and the gene had not been identified or cloned (it was subsequently cloned in 1986).
2. We confirmed that many second cancers developed in the irradiated field after long latent periods, and so they were probably radiation induced.
3. We identified some patients who had second cancers in the radiated field after "low doses" (3500 cGy), which suggested that the cancers were not induced only by high doses of radiation.
4. We identified second cancers in the head/sinuses in patients with bilateral disease who had not undergone radiation but would have fit our definition of radiation induced if they had received radiation. We subsequently reported on these patients alone and suggested a very high incidence of second cancers in patients with bilateral disease who underwent no radiation.
5. We identified patients in whom second cancers developed far distant from the radiation field. Some of these patients were treated with high doses of radiation, others with "low doses" (3500 cGy), and others with no radiation. We speculated that these children might be at higher risk for the development of cancer whether they underwent radiation or not.

These observations propelled us and other centers to elucidate further the impact of the gene effect, exposure to radiation, effect of radiation doses, timing of second cancers, location of second cancers, outcome of second cancers, and the point at which the numbers became large enough for us to calculate relative risks of specific second cancers, allowing us to identify the second cancers that were truly related to the gene effect and the effect of radiation.

Impact of the Gene

Careful studies have demonstrated that patients with retinoblastoma are not at higher risk (lifelong) for any medical problems except cancer. Neither heart disease, accidents, suicides, drug use, pulmonary disease, or gastrointestinal disease...
are at a higher incidence. The retinoblastoma gene clearly predisposes one to cancer, but to nothing else.

Who Is at Risk for Subsequent Development of a Second Cancer?

Much has been learned about the gene since the early 1970s. Some patients affected unilaterally harbor the germinal gene defect whereas others do not. Molecular identification of the gene is an elegant way of differentiating the two, but at the present time (and historically) this information is rarely available. On clinical grounds, the following parameters are usually used to identify unilateral disease in patients who have the germinal mutation and are at risk for developing second cancers:

1. Patients with unilateral disease in whom bilateral disease subsequently develops.25
2. Unilaterally affected patients in whom subsequent independent, new foci of intraocular tumor develop in the same eye (not seeding).20
3. Children born to parents with bilateral27 or unilateral retinoblastoma,28 and in some cases retinomas.
4. Children with disease diagnosed at a young age. There is a 96% chance that a child with diagnosis made in the first month of life has the germinal mutation.29

Our studies of unilaterally affected patients who have the germinal mutation based on these assumptions have revealed that they are at the same risk of developing second cancers as patients with bilateral disease.30 In contrast, patients with unilateral disease who do not harbor the germinal mutation are not at higher risk of developing cancer, whether or not they undergo radiation.31 Patients with retinomas who have never been treated for retinoblastoma are also at risk for developing second nonocular cancers.32

At the present time, we do not know whether specific mutations or genetic alterations of the retinoblastoma gene either predispose patients to subsequent second cancers or to specific cancers. As will be discussed later, there is evidence that specific patients are at risk for developing specific second cancers (sarcomas versus melanomas) but the genetic events that determine this predisposition are not presently known.

What Is the Impact of Radiation on Second Tumor Development?

Studies reported from our group, France, Holland, and England and series reported from other centers worldwide have clearly demonstrated the impact of radiation on these genetically primed patients, including the following effects:

1. An increase in the overall incidence of second cancers.33 Among the largest study ever published, we demonstrated a Kaplan-Meier cumulative incidence of 51% at 50 years in those with the germinal mutation but only a 27% incidence in those at risk who did not undergo radiation (Fig. 1). Qualitatively similar results have been reported from France, Holland, England, and elsewhere. Moll et al.34 have reviewed the subject (as of 1997) and reported that most centers have found similar results. They and a French group35 point out that direct comparison of series is impossible. I have previously outlined the reasons why direct comparisons are impossible.36 Some series report incidence, whereas others report survival. Some include benign tumors, whereas others include only cancers. Some use life-table analysis but others do not. Some have excellent follow-up, but others lose more than half their patients to follow-up. Finally, some series classify midline brain tumors as second tumors, whereas others classify them as “third tumors.”

2. An influence on the timing of second cancers. When Forrest21 wrote on the subject in the 1960s, it was assumed that radiation-induced cancers developed in the radiated field after long latent periods. In general, that has been true in cancer, but not in children with retinoblastoma. Because these children have one defective cancer gene in every cell of the body, it turns out that most of the radiation-related cancers develop after relatively short latent periods. Thus, the cancers that develop in the first 10 years of life are mostly related to the radiation, whereas those in later years are less related to radiation. Our studies on sarcomas,33,35 confirmed recently by the French,37 demonstrate that the timing of sarcomas is predictable. Osteosarcomas of the extremities occur during growth spurts (teenage years) and not before or after. Sarcomas of the head, however, have two distinct peaks: in the first 10 years of life and then with increasing incidence again around the age of 30. Radiation in general appears to increase the incidence of these tumors, but it appears that the radiation given to children younger than 1 year of age greatly increases the incidence of sarcomas in the head during the first 10 years.

3. An influence on the location of second cancers. Without therapeutic radiation, two thirds of the cancers that develop in retinoblastoma are out of the radiation field and one third are within it. In the majority (two thirds) of cases, however, second tumors develop in the radiation field.

4. An influence on the type of second cancer. With radiation, most of the second cancers that develop are sarcomas and brain tumors. In children who do not undergo radiation, most of the tumors are of epithelial origin (e.g., melanomas). In most series, the most common second cancer is a sarcoma, but in series in which radiation was used less often, the most common cancers are epithelial in origin and out of the field of radiation (lung, bladder).38

5. An influence on the survival of the patient. Overall, approximately 50% of patients with second cancers have died of the disease. In our review of 1603 cases, 26% died at 40 years, and death was more frequent in girls (relative risk = 3.9) than in boys (relative risk = 2.2).24 Recently, data from France demonstrated that 45% of the studied patients with second tumors died by 30 years of
Some series reported incidence as the number of cases observed divided by the number at risk. (We also did this in our earlier series.) This greatly underestimates the overall incidence. Over the past 20 years, only Kaplan-Meier life-table analysis has been accepted. To give an example of the importance of this statistical tool, in the same patients in whom we reported a 12% incidence of second cancer, subsequent life-table analysis of the same patients revealed a second cancer incidence more than five times as high!

Follow-up of patients varies greatly in many series. Although life-table analysis can overcome some of this problem, when series are small, the loss of patients to follow-up can significantly distort the data. Desjardines pointed out that in their series from France, the true incidence of second cancers appeared to be either 18% or 68%, depending on what might have happened to the patients who were lost to follow-up. That is why we believe that our series, with 94% long-term follow-up, has great value.

The duration of follow-up is limited in many series. No individual physician has observed these children for 50 years. Forrest had assumed that the second cancers that were radiation induced had the longest follow-up, but we now know that the radiation-induced ones are primarily those with the shortest follow-up. Thus, if a series has only 10, 15, or even 20 year follow-up, the contribution of the gene and that of radiation is not truly appreciated.

Some series analyze risk for all patients and do not analyze separately those who have the germinal mutation or those who were radiated.

In my review of the subject in 1999, I pointed out that there were 14 studies (besides ours) published on more than 50 patients with retinoblastoma and that we had published four large series with more than 1500 patients. Overall, I thought that the series were all similar, but important differences in data collection and use of radiation appeared to have misled some authors to think their series were somehow unique. Here are some of the differences that I pointed out.

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4. Some series analyze risk for all patients and do not analyze separately those who have the germinal mutation or those who were radiated.

5. Some series use incidence of second tumors as an endpoint, and others use death. Some use both.

6. Some (most) series include benign tumors in the incidence, whereas others include only malignant cancers.

7. In some series, midline brain tumors (trilateral retinoblastoma) are included as second cancers, but not in others (some prefer to call them retinoblastoma in the “third eye”). Because 10% of children treated with radiation in our series have trilateral retinoblastoma develop in the first 10 years of life, this is a significant cause of published differences.

8. In some series, second cancers have been grouped by anatomic location, in others by histologic type. In many cases, true identification of the cancer is impossible because no tissue is available for study and some series probably include some metastatic retinoblastomas which are incorrectly listed as second malignancies.

9. Most important, different series have different percentages of children who received radiation; and, as discussed in the next section, the dose and type of radiation used significantly influence second tumor development.

**Impact of Radiation Dose**

As early as 1969 it was recognized that the dose of radiation affects the incidence of second cancers. Sagerman et al. reported that, at doses of 11 to 15,000 cGy, the cumulative incidence was 32%; at 6 to 11,000 cGy, it was 5.5%; and at 6,000 cGy, it was 2.5%. Unfortunately, their follow-up of those with the lowest doses was relatively short, and so they did not appreciate the real incidence at the lower doses, but the incidence became very evident in our study of 1604 patients from New York and Boston who were treated between 1914 and 1984. For this study, we calculated the actual dose received by soft tissue structures (not just the targeted dose for the eye). This was important because, as the energy of the radiation source has changed over the years, the amount of radiation that the bone receives is very different (even if the dose to the eye were the same, which is not the case). We found a stepwise dose-response relationship for sarcomas. This increased risk was evident at all doses studied from 1000 to 6000 cGy. We were able to calculate a relative risk of exposure per Gy of 16.6% for soft-tissue sarcomas and 19.1% for all sarcomas. The odds ratio at 0 to 4.9 Gy was 1.0; at 5 to 9.9 Gy, 1.91; at 10 to 29.9 Gy, 4.6; at 30 to 59.9 Gy, 6.4; and at >60 Gy, 11.7. Thus, those series (such as ours) that had long follow-up of patients who received high doses of radiation have the highest incidence of second cancers. From the Mayo Clinic, Mohney pointed out that their lower incidence of second cancers was probably attributable to the fact that the mean dose of radiation delivered was much lower than that in the New York series. (Even with that difference, their 4-year Kaplan-Meier incidence was 30%)

**Implication of the Age at Which Radiation Is Given**

Our study was the first to look at how the age at radiation influenced the incidence of second tumors. Without radiation, second cancers had developed in 22% of our patients at risk. If radiation was given after the age of 12 months, 32% had second cancers. In patients with disease radiated during the first year of life, 45% had development of second tumors. When we looked at children who had the disease diagnosed and radiated in the first month of life, the incidence was 54% by 20 years of age!

A similar study was repeated by the Dutch group. They too found a marked difference in incidence of second cancers when comparing those who underwent radia-
tion before and after the age of 1 year. At 25 years of age, the cumulative incidence of second cancers was 22% overall, but only 5% in those treated with radiation after the age of 1 year. Although they confirmed the age effect, they speculated that the difference might not be caused by radiation alone, because they do not consider a pinealoblastoma a second cancer. I suspect that radiation is the major cause, because when we looked at the children who had undergone radiation in the first month of life we found no children who had not been treated with radiation who had a second cancer. This observation suggests that it was the radiation at that age that predisposed them to second cancers.

**SUBSEQUENT DEVELOPMENT OF THIRD, FOURTH, AND FIFTH CANCERS**

We have carefully followed our cohort of patients with second cancer to see whether they are at additional risk of developing subsequent malignancies if cured of the second tumor. Because more girls die of second cancers, boys were found to be at greater risk of subsequent cancers. Of the survivors of second cancers, third tumors developed in 22% within 10 years. Of those who survived the third cancer, about half went on to have a fourth cancer and then a fifth cancer. The most common sites for third cancers were soft tissues of the head and skin. The locations and expected ages at which subsequent cancers developed were consistent with the patterns already discussed for second cancers, but it appeared that patients who had sarcomas as a second cancer had them as subsequent malignancies, whereas those who had malignant melanomas as second cancers also had them as third cancers, suggesting a basic genetic propensity that is probably not due to the already identified chromosome 13 abnormalities that caused the retinoblastoma.

**WHAT SECOND CANCERS ARE TRULY INCREASED IN RETINOBLASTOMA SURVIVORS?**

Many, many cancers (>40 cancers) have been reported as second cancers in retinoblastoma survivors, but only relatively recently have we and others been able to determine accurately whether there is a truly increased incidence or just a random happening. The present list of cancers that have been confirmed to be increased in incidence include soft tissue sarcomas, osteosarcomas, brain tumors (benign and malignant), cutaneous melanomas, Hodgkin disease, buccal cavity cancers (salivary gland and tongue), breast cancer in women, lung cancer, and leiomyosarcoma. Recently, it has been shown that the breast cancers in women are related to the very small scatter dose caused by the penumbra when as children they underwent radiation for retinoblastoma. Thus, despite the fact that these cancers are classified as “out of the field” they appeared related to radiation exposure—even in retinoblastoma patients without the RB1 mutation!

**PREVENTION OF SECOND CANCERS**

Since the gene defect is identified and some of the factors that increase the background propensity for second cancers have been identified, we have some suggestions that may minimize the risk of second cancers.

1. Avoid radiation. The impact of therapeutic radiation has already been extensively reviewed.
   a. If radiation is to be given, **avoid high doses**. With present doses, the incidence of second cancers is one tenth that of doses of >6000 cGy.

2. Avoid sun (UV) exposure. Survivors of retinoblastoma are at risk for developing cutaneous (and ocular) melanoma. There is no evidence implicating UV exposure, but until that is clearly studied, we think minimizing UV exposure is reasonable.

3. Avoid cigarette smoking. Our studies have demonstrated that cigarette smoking may be especially carcinogenic in children with the retinoblastoma gene defect. There has been a suggestion that second-hand smoke may also be implicated.

4. Avoid human growth hormone. It has recently been demonstrated that long-term survivors of childhood cancer who receive human growth hormone are at higher risk for the subsequent development of sarcomas. We reported one such case of an osteosarcoma that developed in a child who received human growth hormone for short stature as a result of pituitary dysfunction after external beam radiation.

5. Monitor patients with retinoblastoma who have subcutaneous lipomas carefully. We have demonstrated that patients with hereditary retinoblastoma have an increased chance of developing lipomas (relative risk = 8.2). In addition, the patients who do have lipomas have a greater chance of developing a second cancer than those without. The molecular explanation for this genotype–phenotype association is presently unknown.

6. Avoid systemic chemotherapy. Two studies have specifically looked at the contribution of systemic chemotherapy to the development of second cancers, and both have implicated the chemotherapy. The first, from England, suggested that cyclophosphamide exposure correlates with more second cancers. A recent retrospective review from
France suggested that exposure to triethylene melamine (TEM) was associated with a significant increase in second primary tumors outside the field of radiation.\(^7\)

There has been great concern about this subject, as all centers worldwide have attempted to avoid external beam radiation in the hope of minimizing second cancers and have used systemic chemotherapy instead. Combinations of vinblastine, etoposide, and carboplatin have been used. Unfortunately (in patients with cancer other than retinoblastoma), secondary acute myelogenous leukemias (SAML) are well recognized as a complication of exposure to platinum-based drugs.\(^8\) Etoposide causes a specific genetic derangement that also results in secondary AML.\(^9\) Before the introduction of chemotherapy, there had never been a child with retinoblastoma in whom AML developed as a second neoplasm. A recent review has demonstrated 12 such cases.\(^7\) Most of these children died soon after the diagnosis of the leukemia, and almost all had received epipodophyllotoxins and/or alkylating agents. Only soon after the diagnosis of the leukemia, and almost all had received epipodophyllotoxins and/or alkylating agents. Only.

INFORMING PARENTS AND PATIENTS ABOUT THEIR RISK OF SECOND CANCERS

We routinely inform parents of children with retinoblastoma and the patients themselves (when older) of the risk of developing second cancers. We do this in conversations, through our Web site (http://www.retinoblastoma.com), and with the use of teaching cards (see Ref. 35) and a "results letter." When we studied the impact of that letter, we found that feelings of guilt, perhaps due to a sense of responsibility for causing the tumor in their child, or simply for having the tumor, were prominent in both parents and children. Parents felt more guilty than the patients themselves. Less education correlated with greater feelings of anger, anxiety, guilt, and being overwhelmed. However, 72% of parents (and children?) thought the letter was “very” to “extremely useful,” though 28% felt “frightened,” 27% anxious, 25% sad, and 15% overwhelmed.\(^61\) As more and more is learned about these cancers, physicians must explore the most effective and least frightening way of informing parents and patients about their lifelong risk of second cancers.

References