Are Ocular and Ocular Adnexal Cancers Overdiagnosed? Historical Perspectives on Diagnosis

Applying the term overdiagnosis to cancer reflects a conceptual shift in thinking about cancer as a neoplastic proliferation based on histopathological criteria to a disease that, if left untreated, becomes symptomatic and results in morbidity or death. During the past decade, select cancers — correctly diagnosed historically as cancer — would have gone undetected during a patient’s life (ie, remained clinically silent) if it were not for screening programs. The most robust evidence for overdiagnosis comes from randomized clinical trials of cancer screening and observational studies. For some cancers, the results of randomized trials have revealed no compensatory decrease in cause-specific mortality rates among a screened cohort of patients. Observational studies complement these findings, demonstrating a rapid rise in cancer diagnoses after screening programs are instituted without any long-term change in cancer-specific mortality rates.

The notion that early detection will lead to early treatment and reduced rates of cancer-specific mortality is intuitively appealing. Although this ideal does occur with some cancers like colon and cervical cancer, this is not universally the case. In industrialized countries, the overdiagnosis phenomenon involves mostly prostate, breast, renal, and thyroid cancers. Given that these seemingly counterintuitive findings may be at odds with compelling anecdotes of success, the discussion about cancer screening has become controversial.

Overdiagnosis arises because cancer screening uncovers a reservoir of indolent tumors that would have otherwise gone unnoticed throughout life. Early detection of either nonprogressive or slow-growing cancer gets caught up in this net, which is larger if precursor lesions and in situ neoplasia are factored into the screening process. For select patients, death from other causes will occur during the period of cancer inexpression. Because of tumor latencies and competing risks of mortality, some patients screened for cancer are subject to the costs and adverse events of treatment without any prospect of benefit.

However, the conundrum of overdiagnosis involves applying this epidemiological perspective to individual patients. At the time of screening diagnosis, it may be impossible to distinguish persons with indolent, nonprogressive lesions from those with potentially lethal cancers. The problem of overdiagnosis has surfaced in ophthalmology before but not as the result of epidemiological sleuthing and certainly not in the context of screening programs. Claims of overdiagnosis were raised because there was a sense of incongruity between the lesions observed under the microscope and the commensurate treatments. A few examples illustrating this phenomenon are offered.

Beginning in the late 1930s, Reese solidified the idea of conjunctival melanosis as a precursor lesion to conjunctival melanoma. He distinguished it from congenital melanosis and termed it precancerous melanosis. Acknowledging that its progression to melanoma is often protracted, Reese estimated that approximately 17% of cases of precancerous melanosis become cancerous (ie, conjunctival melanoma) within 5 years and that conjunctiva melanoma had a mortality rate of at least 40%. Based on clinical and pathological observations, he favored orbital exenteration for some early stages of melanosis when it appeared flat. Few ophthalmologists were as influential in establishing practice guidelines as Reese, and few pathologists had much proficiency in interpreting findings on conjunctival biopsies as he did.

By 1966, Zimmerman accumulated considerable experience with conjunctival melanosis treated by radical surgery. He grew concerned that orbital exenteration might not be justified for some cases of precancerous melanosis because, to him, the histological findings suggested low potential for aggressive growth or distant metastasis. He proposed a method for evaluating acquired melanosis based on conjunctival biopsy that stratified risk for melanoma progression. This strategy was formally presented by Zimmerman about a decade later.

Folberg et al would later introduce new terminology for conjunctival intraepithelial melanocytic neoplasia (ie, primary acquired melanosis with and without atypia) and then test the prognostic capabilities of different histopathological variables. These studies tempered the role that radical surgery played in the management of acquired conjunctival melanosis by introducing a means of gauging the likelihood of progression.

Jakobiec and Silbert perceived a similar challenge with the overdiagnosis of iris melanoma. They used a retrospective, clinicopathological study to test their hypothesis and then published their results in 1981 with the provocative title “Are Most Iris Melanomas Really Nevii?” Just as Zimmerman had emphasized that
the diagnosis of precancerous melanosis inflated the risk of cancer in the minds of clinicians, Jakobiec and Silbert\(^{10}\) believed taxonomy obstructing effective communication. Seldom have charges of cancer overdiagnosis been so unambiguously stated.

The dilemma of how best to classify indolent, melanocytic tumors of the iris did not simply materialize. Inadequacies with the classification of melanocytic tumors of the uveal tract had been known since the 1960s, which is when it was realized that the original system developed in 1931 by Callender\(^{17}\) did not include nevus (Table).\(^{18-20}\) In 1978, McClean et al\(^{18,19}\) addressed this oversight by studying 105 spindle A melanomas of the choroid and ciliary body that had already been histologically diagnosed by expert consultants. After reviewing each case, they found that 15 cases (14.3%) of spindle A melanomas were actually cytologically benign nevi.\(^{18,19}\) Among this group, no evidence existed of spread or tumor-related death.\(^{18,19}\) Another 75 tumors (71.4%) were diagnosed as spindle cell melanomas based on cytological features.\(^{18,20}\) They consisted of mixtures of spindle A and B melanocytes, and they had a prognosis similar to those previously reported as spindle B melanoma.\(^{18,20}\) Another 15 tumors (14.3%) contained some proportion of epithelioid melanocytes and had a prognosis similar to a mixed-cell type.\(^{18}\) These cases were accordingly reclassified as mixed-cell type melanomas.\(^{18}\) The so-called “classic” spindle A melanocyte fell along a cytological spectrum, and it could be found in both nevi and spindle melanomas.\(^{20}\) The authors recommended that choroidal and ciliary body nevus be added to the spectrum of diagnoses and that the distinction between spindle A and B types of melanomas be dropped (see Table).\(^{18,20}\)

The approach to testing the perception of the overdiagnoses of cancer and precancer that these investigators took was similar. Based on histopathological observations, they proposed improved means of predicting clinical behavior and then tested those algorithms against clinical outcomes retrospectively obtained. In each situation, pilot studies supported their premises of overdiagnosis. However, uncommon cancers with prolonged clinical courses are difficult to study. Nonetheless, the boundary between indolent and aggressive neoplasia examined by these investigators must always be scrutinized in order to improve diagnostic precision.

These examples emphasize a critical difference between the overdetection of cancer, related to excessive cancers found in screening programs, and overdiagnosis, which applies to pathologically verified cancers (or in situ disease) of an indolent type.\(^{3}\) These overdiagnoses are not the result of misdiagnoses; rather, the diagnoses satisfied the standards for precancerous melanosis, iris melanoma, and spindle A choroidal and ciliary body melanoma that existed at the time. What was in dispute was whether the diagnostic categories were too broad, harboring lesions with little propensity for growth or metastatic spread and no risk of death.

Epidemiological deduction provides a belated defense against overdiagnosis, but this safeguard is ill suited for uncommon cancers or ones not subject to screening programs like those in and around the eye. However, the legacy of overdiagnosis of ocular and ocular adnexal cancers may unconsciously linger in the minds of many clinicians, possibly explaining the intensity with which ocular oncologists have critiqued new systems of cancer staging.\(^{21}\) Ever since the seventh edition of the American Joint Committee on Cancer Staging System was published,\(^{21}\) a flurry of studies has assessed the updated algorithms.\(^{22-26}\) Although most have found that the modifications are based on sound evidence and are thusly improved, some already anticipate supplementing them with new technologies.\(^{27}\)

Establishing the interface of benign and malignant and indolent and aggressive cancers has been the province of anatomical pathologists for a century, but this jurisdiction is yielding to molecular “pathologists” who have at their disposal the genetic makeup of tumors from which to work. The genetic signatures of primary ocular cancers (eg, retinoblastoma, uveal

<table>
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<tr>
<th>Original Grouping(^{17})</th>
<th>Modified Classification(^{18-20})</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Spindle A–type melanoma</td>
<td>Melanocytic nevus</td>
<td>Callender(^{17}) did not consider benign category</td>
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<tr>
<td>Spindle B–type melanoma</td>
<td>Spindle cell melanoma</td>
<td>Not synonymous with nevus</td>
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<tr>
<td>Epithelioid-type melanoma</td>
<td>Epithelioid type</td>
<td>Spindles A and B–type melanocytes commonly found together</td>
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<td>Mixed spindle- and epithelioid-type melanoma</td>
<td>Mixed spindle- and epithelioid-type melanoma</td>
<td>Worse prognosis</td>
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<td>Fascicular pattern melanoma</td>
<td>Spindle cell melanoma</td>
<td>Prognosis falls between spindle and epithelioid types of melanoma</td>
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<tr>
<td>Necrotic melanoma</td>
<td>Necrotic melanoma</td>
<td>Tumors too necrotic to classify</td>
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Table. — Histological Classification of Choroidal and Ciliary Body Melanomas
melanoma) may forecast risk with greater reliability and precision than before and also provide insights into targeted therapies.\textsuperscript{27,28}

In conclusion, timely, accurate diagnosis and the ability to forecast the behavior of malignancy are the goals of clinical practice and are central themes running through papers in this issue of *Cancer Control*. Clinical decision-making in ocular oncology may continue to rely on histopathological parsing to minimize overdiagnosis, but predicting the biological behavior of cancer will increasingly depend on molecular-based strategies as we look toward the future.

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References