Cancer Overdiagnosis: Pathologists in the Dock

To the Editor.—We read with interest Dr Schnadig’s thought-provoking editorial on thyroid cancer overdiagnosis in which she questions whether “pathologists are aiding and abetting the epidemic.”1 We wish to expand the discussion by highlighting an area where pathologists are directly responsible for cancer overdiagnosis.

Pathologists generally submit “background blocks” of macroscopically normal tissue from excision specimens. While this may have clinical utility in some settings, such as assessment of background kidney parenchyma from a nephrectomy specimen for unsuspected glomerular disease, this is often a waste of resources and may significantly contribute to cancer overdiagnosis. The latter is best illustrated by 2 common scenarios.

When a patient with Graves disease with failed medical therapy undergoes total thyroidectomy to control hyperthyroidism, it is recommended that at least 7 sections be submitted for histologic examination if no focal abnormality is identified.2 It is not rare for microscopic foci of papillary carcinoma to be found in these blocks but these non–mass-forming “tumors” are very unlikely to cause any clinical problems for the patient, who is now burdened with a diagnosis of thyroid cancer. The reported frequency of thyroid cancer in Graves disease varies from 0.5% to 15%.3 However, this includes grossly identified lesions, so the incidence of macroscopically occult cancers would be lower.

Although rare cases of synchronous distant metastasis from papillary thyroid microcarcinoma have been described,4 the scientific and clinical rationale behind sampling grossly normal thyroid tissue in this scenario is questionable. Pathologic parameters are for stratifying patients, with different outcomes predicted for those who are positive or negative for the parameter. However, in the scenario described above, identification of focal papillary microcarcinoma is essentially a chance phenomenon in a block randomly selected for histologic examination. Moreover, some cases reported as negative for malignancy would have undetected focal carcinoma deeper in the tissue block. Finally, these patients have already been treated with total thyroidectomy so detection of even multifocal microcarcinomas is unlikely to have any management implications.

An alternative approach could be to examine the slices carefully with a hand lens and sample only grossly abnormal areas. In cases with no focal abnormality, a macrophotograph would be a better record than a few random sections.

A more clinically significant issue relates to tissue sampling of transurethral resection of prostate (TURP) specimens from patients with no clinical suspicion of prostate cancer. The College of American Pathologists recommends submitting 11 sections from a 25-g TURP specimen.5 As in the previous example, these men have undergone surgery to treat symptoms that could not be controlled by medical therapy. If retention was due to cancer, then most of the chippings would be cancerous and very limited tissue sampling would be sufficient to identify tumor. The more extensive tissue sampling protocol is designed to detect clinically occult cancer and hence it is a form of cancer screening with low-volume, low-grade, generally clinically insignificant cancer detected in about 5% of these specimens.6 Even if they do not undergo radical therapy, these men are often managed with active surveillance protocols that could have significant impact on their finances and mental health.

The second scenario also raises a significant ethical issue because a man who had declined prostate cancer screening (Prostate-Specific Antigen test) could have his TURP specimen screened for occult cancer without his informed consent!

Random sampling of morphologically normal tissues for histologic examination may pick up a few cancers, but most of these are likely to represent overdiagnosis, and such sampling protocols can have significant resource implications for hard-pressed pathology laboratories.

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1. Schnadig VJ. Overdiagnosis of thyroid cancer: is this not an ethical issue for pathologists as well as radiologists and clinicians? Arch Pathol Lab Med. 2018;142(9):1018–1020.

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In Reply.—While my editorial deals with issues owing to events that occur prior to surgical excision, Shah et al discuss potential overdiagnosis and ethical quandaries generated by evaluation of multiple sections from organs removed for nonneoplastic conditions. As they point out, some consider this practice ipso facto screening for incidental carcinomas,1 and the subject is worthy of consideration and debate. I am pleased that this issue is being raised and hope that clinicians, surgical pathologists, and patients will continue to address this problem. Radiologists now have to contend with a similar conundrum caused by diagnostic computerized tomograms (CTs) and other imaging examinations that incidentally cut through the thyroid gland or other organs during evaluation of problems unrelated to those organs.2 This too could be viewed as unsolicited screening. Both histopathologic and radiologic incidentalomas have harmful potential given that most incidentalomas are benign and many that are called malignant are indolent or non-
progressive. The word *malignant* can be terrifying, and *risk of malignancy* equally scary.

Clearly, primary care givers, specialists, surgeons, radiologists, and pathologists are now facing dilemmas and controversy regarding how to maximize patient benefit and minimize harm. A potential tool for limiting detection and overtreatment of incidentalomas is shared decision making (SDM). Shared decision making is a 30-year-old idea that is reemerging as a patient-centered technique for discussion of screening test risks and benefits and holds promise despite limitations imposed by physician time constraints and cognitive bias.\(^3\)–\(^5\) Shared decision making is already proposed for use prior to mammography and CT lung cancer screening. Recently, D’Agostino et al.\(^6\) investigated patients’ decision-making process in choosing between surgery and active surveillance for thyroid papillary microcarcinoma. This interesting study sets the stage for thyroid cancer SDM. These authors confirmed that, to patients, “Just the word ‘cancer’ is scary.” Can SDM be used to limit detection of incidentalomas? After they have been provided with nonbiased, evidence-based risk/benefit information and an opportunity to ask questions of their physicians, could not this tool be used to allow patients to elect to limit or forego follow-up procedures following detection of incidentalomas via histology or imaging? Also, could not pathologists and radiologists be trained to participate in SDM prior to fine-needle aspiration, surgical procedures for benign conditions, and imaging studies? At least, this is something to ponder.

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Letters to the Editor

**In Response to “Overdiagnosis of Thyroid Cancer: Is This Not an Ethical Issue for Pathologists As Well As Radiologists and Clinicians?”**

To the Editor.—We read with interest Dr Schnadig’s\(^6\) article on overdiagnosis of thyroid carcinoma. Pathologists have recognized this problem for at least a decade,\(^2\) and have actively worked to reduce this incidence by a variety of means, including the introduction of noninvasive follicular tumor with papillary-like features (NIFTP).\(^3\) Preliminary data suggest that these efforts are succeeding.\(^4\) We agree by all means that pathologists and cytologists should be actively engaged in trying to educate clinicians and patients alike about the true risks associated with the lesions they are treating.

However, we strongly disagree with the suggestion that reporting the risk of malignancy (ROM) in an indeterminate thyroid fine-needle aspiration report should be discouraged.\(^1\) Reporting ROM was introduced\(^2\) around the time of the original description of the Bethesda System for Reporting Thyroid Cytopathology\(^3\) as a way to allow more accurate comparison of the performance of individual cytopathologists and laboratories for both quality assurance and research purposes. In our view, reporting the ROM along with the standardized terminology of the Bethesda System has been wildly successful. It is certainly much more effective than trying to figure out what a diagnosis of atypical or indeterminate might mean from a cytopathologist or laboratory that uses nonstandardized terminology for which the risks have not been documented. Indeed, the evidence that pathologists are actually succeeding at reducing the overdiagnosis of thyroid carcinoma is strongly supported by data that explicitly use ROM.\(^3\) The only limitation we see with its current use is that it would be much more informative if individual laboratories reported the ROM calculated with data from their own individual laboratories rather than the ROM from published national studies. Either way, however, is much better than reducing the information we provide for our clinicians and patients by not reporting ROM at all.

However, what really seems to bother Dr Schnadig is that the ROMs that are reported are too high. In this regard we agree. The most recent version of the Bethesda System continues to report ROMs for indeterminate aspirates that are similar to those in the first edition and do not account for NIFTP. These data are no longer relevant and are actively misleading. The second edition of the Bethesda System does, however, also include a table in which NIFTP is taken into account. Our experience with more than 15,000 aspirates and 2000 resections\(^5\) is that the ROM for indeterminate aspirates in our laboratory is at the very lowest end of the range reported in the Bethesda System. We believe that as pathologists continue to become more comfortable diagnosing NIFTP, the reported ROMs for indeterminate thyroid aspirates will continue to decrease, and the difference in risk between an indeterminate and a benign aspirate will continue to shrink. As a result, defining exactly what the ROM of a benign aspirate actually is\(^8\)–\(^11\) turns out to be crucial. Both clinicians and cytologists often confuse the risk of clinically significant disease (ROCSD, however one wishes to define it) with the ROM. The data clearly show that the ROM of a benign aspirate is about 3% (even when NIFTP is taken into account, because most of these cases are the result of inadequate sampling of classical malignancies), whereas the ROCSD based on clinical follow-up of patients with benign aspirates approaches zero. The difference between 0 and 3% may be very important to both patients and researchers. Most, if not all, of the current molecular tests do not achieve sensitivities of 100% for their benign category.

Given the confusion between ROM and ROCSD, our preference would be to report both of them for our indeterminate thyroid aspirates, and thus give...