Review Article

Overdiagnosis of Thyroid Cancer:

Answers to Five Key Questions

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Thyroid cancer fulfills the criteria for overdiagnosis by having a reservoir of indolent cancers and practice patterns leading to the diagnosis of incidental cancers from the reservoir. The occurrence of overdiagnosis is also supported by population-based data showing an alarming rise in thyroid cancer incidence without change in mortality. Because one of the activities leading to overdiagnosis is the workup of incidental thyroid nodules detected on imaging, it is critical that radiologists understand the issue of overdiagnosis and their role in the problem and solution. This article addresses 1) essential thyroid cancer facts, 2) the evidence supporting overdiagnosis, 3) the role of radiology in overdiagnosis, 4) harms of overdiagnosis, and 5) steps radiologists can take to minimize the problem.

Key Words: Thyroid cancer; overdiagnosis; screening; incidentaloma; incidental thyroid nodule.

Overdiagnosis is the detection of a disease that is not destined to cause symptoms or result in death. Thyroid cancer represents one of the best examples of overdiagnosis. It has become one of the most rapidly increasing cancer diagnoses in the United States and now ranks as the fifth most common cancer in women (1,2). The recent rate of growth in incidence is particularly alarming. The incidence of papillary thyroid cancer has doubled in the last decade, whereas before 2002, the incidence of papillary thyroid cancer doubled over a 30-year period (1). And yet, these trends are dwarfed by the experience in South Korea where opportunistic ultrasound screening for thyroid cancer is offered as an inexpensive "add-on" during screening for other cancers. This has resulted in a 15-fold increase in thyroid cancer incidence in an 8-year period with no change in mortality (3).

One of the activities leading to overdiagnosis of thyroid cancer is the workup of incidental thyroid nodules detected on imaging (4–6). Thus, radiologists are a key part of the problem and solution. In March 2012, the National Cancer Institute (NCI) convened a meeting to evaluate the problem of overdiagnosis (7). An important recommendation made by the working group was that the physician, patient, and public need to be aware that overdiagnosis is common. For radiologists, this means being informed about the issue of overdiagnosis and interpreting incidental findings on imaging studies with consideration of cancer biology and epidemiology. This article describes thyroid cancer overdiagnosis for radiologists in the format of five questions. We address 1) essential thyroid cancer facts, 2) the evidence supporting overdiagnosis, 3) the role of radiology in overdiagnosis, 4) harms of overdiagnosis, and 5) steps radiologists can take to minimize the problem.

WHAT ARE THE ESSENTIAL FACTS ABOUT THYROID CANCER?

Thyroid cancer ranks as the ninth most common cancer in the United States and the fifth most common cancer in women (2). It is estimated that there will be more than 62,000 new cases of thyroid cancer in 2014, but the number of deaths in 2014 will be much lower at 1890 (2). In fact, thyroid cancer has the lowest mortality rate among the top 10 cancers, and as a result, more than half a million people in the United States are currently living with thyroid cancer (2).

There are four main types of thyroid carcinomas. Papillary and follicular carcinomas arise from the follicular epithelial cells and are known as differentiated thyroid carcinomas. Differentiated thyroid cancers have an excellent prognosis, with a 10-year survival rate >95% for papillary carcinoma and 85% for the follicular type (1,8). Medullary thyroid carcinoma arises from neuroendocrine "C" cells and has a survival rate of 75% at 10 years (8). Anaplastic carcinoma is an aggressive undifferentiated tumor typically occurring in the elderly with a median survival of 9 weeks and a 5-year survival of 7% (9). The most common histology is papillary carcinoma, which represents 88% of all thyroid malignancies (10).

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Radiologists may have a skewed view of the aggressiveness of thyroid malignancy because cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) is only performed for suspected locally invasive cancers or patients with recurrence (11). However, these "bad actors" represent the minority of thyroid cancers. Only 4% of thyroid cancers have distant metastases, and the rate of thyroid cancer recurrence is low, ranging from 7% to 14% (2,12,13). Although the 5-year survival for thyroid cancer patients with distant metastases is poor at 55%, patients with regional (nodal) metastases still have excellent survival at 98% (2).

ARE WE REALLY SEEING OVERDIAGNOSIS OF THYROID CANCER?

The term "overdiagnosis" has been used to describe excessive diagnosis on the part of clinicians on the basis of clinical criteria (eg, Lyme disease, attention deficit hyperactivity disorder), but in 1993, Black and Welch (14) proposed a very different mechanism for overdiagnosis and identified this to be occurring with certain cancers. They argued that advances in diagnostic technologies were revealing previously undetectable abnormalities—some of which were not destined ever to produce symptoms or death—thus leading to overestimations in both disease prevalence and the benefits of therapy. In 2010, they outlined two prerequisites for cancer overdiagnosis: presence of a subclinical disease reservoir and activities leading to detection of cases from the disease reservoir (15). They added that overdiagnosis could not be proven in an individual, but population-based evidence supports overdiagnosis when there is a mismatch in rates of change between incidence and mortality on a large scale. These three tenets of overdiagnosis are present for thyroid cancer.

A Mismatch in Trends in Incidence and Mortality

One of the first studies to raise the problem of thyroid cancer overdiagnosis is by Davies and Welch (1), who reported incidence and mortality data for thyroid cancer from the NCI's Surveillance, Epidemiology, and End Results (SEER) Program. They saw a mismatch between trends in incidence and mortality: the incidence of thyroid carcinoma increased by a factor of 2.4 from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002, whereas mortality rate was unchanged and extremely low at 0.5 per 100,000 (1). A second article from the same authors provided updated data through 2009 that showed incidence of thyroid cancer was continuing to grow at an even greater rate, with women disproportionately affected by the problem compared to men. The incidence of thyroid cancer in 2009 was 14.3 per 100,000, which represented a quadrupling in incidence in 36 years. Again, there was no change in the mortality rate, which was now 29 times lower than the incidence (16).

Davies and Welch also found that change in incidence differed by thyroid cancer histology and size. They reported that papillary carcinoma contributed almost entirely to the overall growth in incidence for thyroid cancer and that 87% of the excess papillary carcinomas were ≤2 cm (1). Other investigators also studied the SEER database and determined that among the various size and histologic subgroups, the incidence of subcentimeter papillary cancers was growing at the fastest rate, doubling every 6 years from 1988 to 2009 (10). This disproportionate increase in smaller asymptomatic and less-aggressive papillary thyroid cancers further supports the case of overdiagnosis. If there were a true increase in thyroid cancer incidence because of changes in risk factors or other unidentified causes, incidences for all cancer sizes would have increased at similar rates, with corresponding increases in mortality.

Those who argue against the case of overdiagnosis propose that the stable mortality could be due to the early diagnosis of thyroid cancer and improved treatments. However, if early diagnosis were favorable, we would expect a decrease in mortality after a lag period. This has not been seen despite more than 30 years of data. The stable mortality rates are also unlikely to be explained by improvements in treatment because the reduction in thyroid cancer deaths attributable to improved treatments would have had to exactly match the increased cancer incidence. If improvements in treatment occurred too fast, the mortality line would drop. If improvements occurred too slowly, the mortality line would have risen. For advanced-stage thyroid cancer, there have been new therapies, such as tyrosine kinase inhibitors, redifferentiation therapy, and gene therapy, but there is no substantial evidence in clinical studies that these new treatments have changed cancer-specific survival or mortality (17).

A Reservoir of Clinically Silent Cancers

Thyroid cancer meets the overdiagnosis prerequisite for having a reservoir of subclinical cancers. Cancers in this reservoir will not progress or will progress so slowly that the patient will die from other causes. The best evidence for how commonly patients die *with* rather than *from* thyroid cancer is from autopsy studies. Although there are dozens of studies documenting incidental thyroid cancers on autopsy, the study by Harach et al. is one of the best studies because it was systematic. They examined 2.5-mm-thin sections through the thyroid gland in 101 autopsy patients and found that 36% of adults harbored occult papillary thyroid cancers ranging in size from 0.15 to 14 mm (18). They proposed that the prevalence could be even higher given that many more occult cancers could potentially be missed by the thickness of their sections. Another interesting observation in the study was that the size of cancers did not correlate with the age of the autopsy patient, suggesting that small cancers were either -stable throughout life or that they developed and regressed (18). Harach et al. concluded that occult papillary carcinoma could be regarded as a normal finding and suggested changing cancer terminology to reflect the indolent behavior of these small occult tumors. Their study was published in 1985, and in recent years, the NCI's working group has also