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EDITORIAL – BREAST ONCOLOGY

Treatment Intensity for Mammographically Detected Tumors: An Alternative Viewpoint

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In a nice article in this issue of the *Annals*, Elder et al. present a single-institution experience describing the characteristics and treatment of breast cancers detected among patients participating in the Australian national breast cancer screening program compared with those who did not. The results are very similar to what is seen in almost every hospital in the world with a mature mammography screening program; the screen-detected cancers are smaller and require less treatment. Epidemiologists have been telling us for years, however, that these kind of single-institution studies are subject to lead time, length time, and overdiagnosis bias. Until recently, most of us thought that these were fairly minor effects that would only be important if we wanted a very precise quantification of the benefits of mammography. We know today, however, that these are very large effects that can easily explain most, or even all, of the perceived benefit of screening mammography.

Lead time is the time between when a cancer can be detected on mammogram and when it would become apparent clinically. Lead time bias must be considered when comparing survival between patients with mammographically detected tumors and clinically detected tumors. For example, if the lead time of a group of patients is 5 years, the patients with mammographically detected tumors will live 5 years longer than patients with clinically detected tumors, without changing the natural history of the disease at all.

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In the 1970s, when we thought that breast cancer was basically one disease, it was estimated that the average lead time was 3 or 4 years.[1] Although we knew that some tumors grew a little faster than others, we assumed that the individual lead times were normally distributed around the mean. Today, we realize that breast cancer consists of many heterogeneous diseases, and rather than being normally distributed, there are a large number of fast-growing tumors with very short lead times under 2 years and another large number of very slow-growing tumors with long lead times between 10 and 20 years or even longer.[2]

Length time bias refers to the fact that screening mammography tends to diagnose slow-growing tumors much more efficiently than fast-growing tumors.[3,4] This is understandable, because a single mammographic study is not perfect and detects only a fraction of cancers that are actually present. For a tumor with a lead time of over 10 years, annual mammography has at least ten chances to detect the tumor before it becomes clinically apparent, whereas for a tumor with a lead time of less than 2 years, mammography has either 0 or 1 chance to detect that tumor. This explains the common observation that mammographically detected tumors tend to be low-grade and hormone receptor-positive, whereas clinically detected tumors tend to be high-grade or triple-negative.[3,5] It also explains why detection by mammography is an independent favorable prognostic variable, even when adjusted for tumor size and other known risk factors.[6]

Overdiagnosis bias refers to the detection of tumors by screening mammography that will not become clinically apparent during the patient's lifetime. The best way to think of this today is not that a tumor is totally incapable of progression, but that its lead time is longer than the life expectancy of the patient. For tumors with lead times between 10 and 20 years, a significant percentage of patients, especially elderly women, will die of something else before the tumor can become clinically apparent; this,

therefore, renders their breast cancer overdiagnosed. Lead time, length time, and overdiagnosis are all interrelated. Since the widespread adoption of screening mammography, small tumors less than 2 cm have increased in incidence over three times more than large tumors have decreased.[7] The small tumors have an excellent prognosis, not because they were detected early, but because they are slow-growing, biologically favorable, and have long lead times. In contrast, the aggressive tumors have short lead times and are rarely found on screening mammography. This explains both how screening mammography causes overdiagnosis and also why the benefit of mammography is limited.[2]

Elder et al. attempted to do a sensitivity analysis where they adjusted for the effect of overdiagnosis. But did they do that adequately? A common misconception is that the problem of overdiagnosis is confined largely to in situ disease. The largest amount of overdiagnosis, however, is actually in low-grade, hormone receptor-positive, invasive tumors. In the recent study of SEER data by Welch et al., the overall rate of overdiagnosis was 37%, but of this, 42% was caused by DCIS, 33% by invasive tumors under 1 cm in size, and 25% by invasive tumors between 1.0 and 1.9 cm.[7] In a recent analysis of breast cancer screening in the Netherlands among women age 50–74 years, there was an overall rate of overdiagnosis of 32%, which corresponded to a rate of 52% among the screened patients; 26% of this was due to DCIS and 74% due to invasive tumors under 2 cm.[8] Elder et al. considered all DCIS overdiagnosed but only included 6% of invasive cancers, all under 1 cm, in the overdiagnosed group. Of course, the overdiagnosed DCIS will not affect treatment of invasive cancers. Excluding only 6% of invasive cancers should be considered a minimal, token effort at adjusting for overdiagnosis.

There are some very good clues from the data in the Elder article that their incidence of overdiagnosis among invasive cancers is considerably higher than the authors realized. It is known that 55% of women participate in the Australian breast cancer screening program and that 45% do not; therefore, without overdiagnosis, we would expect that 55% of the invasive cancers would occur among screeners. Instead in their study, 76% of invasive cancers were in the screening population; only 24% of the cancers arose in the 45% of women who chose not to be screened. Table 1 shows three estimates of overdiagnosis of invasive cancers based on characteristics of the patients in the screened and unscreened groups. As can be seen, to get the screened group down to 55% of the total would require removing 298 overdiagnosed invasive cancers, 47% of the entire group or 62% of the screening detected cancers.

A second clue involves the increased incidence of low-grade and hormone receptor-positive tumors among the screened group. This is not due to tumors becoming more poorly differentiated or losing hormone receptors during growth but rather to excess detection of these slow growing tumors by mammography.[3,9] The biological characteristics of the NRS (not recently screened) group reflect the distribution of tumors that are clinically important; the amount of excess low-grade and hormone receptor-positive tumors in the screening group can be used to provide a good estimate of overdiagnosis in this group. Among the NRS group, 80% were estrogen receptor (ER)-positive, whereas among the screened group, 88% were ER positive. As shown in Table 1, to get the screened group down to the 80% seen in the NRS group, would require removing 190 overdiagnosed ER positive tumors, or 40% of all screening detected invasive cancers. Similarly, the percent of grade 1 and grade 2 tumors in the screening group was 27 and 42% compared with 10 and 39%, respectively in the NRS group. To get the screened group down to the same distribution of grade as the NRS group would require removing 91 overdiagnosed grade 1 cancers and 84 overdiagnosed grade 2 cancers, or 39% of all screening detected invasive cancers. The fact that independent estimates using ER and grade both came up with essentially the same estimate for overdiagnosis supports the validity of this methodology.

What effect does this have on treatment intensity? Table 2 shows the likely treatments that would be recommended for invasive tumors with the amounts of overdiagnosis that are suggested by the data and consistent with multiple other studies.[7,8,10] It is assumed that the overdiagnosed cancers were node-negative and were treated with breast conservation and sentinel node biopsy. As the percent of overdiagnosis increases and the indolent cases are removed, the treatment intensity for the remaining true cancers in the screening arm increases and approaches that of the NRS group. The percent receiving adjuvant chemotherapy and hormonal therapy is virtually identical to the NRS group. It appears that, even with the correction, mammography does cause a slight reduction in the percent requiring mastectomy or axillary dissection. This is balanced, however, by tremendous overtreatment of the overdiagnosed cancers. All of these 190 cases received breast surgery and hormonal therapy, 98% of them received sentinel node biopsy, and 88% received radiation therapy, all of which in retrospect may not have been necessary.

Recent articles emphasize that we must weigh the benefits of mammographic screening against its risks.[11] There is fairly widespread agreement that the main benefit from mammography is approximately a 19% reduction in breast cancer mortality.[11] This is not the 75–90% reduction that we had initially hoped for and that many physicians and

TABLE 1 Three estimates of overdiagnosis of invasive cancer based on characteristics of the patients in Elder's screened and unscreened group

	Actual not recently screened group	Actual mammography group	Models removing hypothetical overdiagnosed cancers from the mammography screening group			
			True cancers	Overdiagnosed cancers	% overdiagnosis overall	% overdiagnosis screening group
Distribution of screened and unscreened cases	150 150/631 = 24%	481 481/631 = 76%				
Remove cases from screened group to achieve 55%	150 150/333 = 45%		183 183/333 = 55%	298	298/631 = 47%	298/481 = 62%
Estrogen receptor						
Positive	118 (80%)	423 (88%)	233 (80%)	190	190/628 = 30%	190/481 = 40%
Negative	29 (20%)	58 (12%)	58 (20%)	0		
Total	147[a]	481	291	190		
Grade						
1	13 (10%)	118 (27%)	27 (10%)	91	175/580 = 30%	175/445 = 39%
2	52 (39%)	188 (42%)	104 (39%)	84		
3	70 (52%)	139 (31%)	139 (51%)	0		
Total	135[b]	445[c]	270	175		

[a]Three patients missing estrogen receptor

[b]Fifteen patients missing grade

[c]Thirty-six patients missing grade

TABLE 2 Likely treatment for invasive cancers with various estimates of overdiagnosis

	No overdiagnosis	25% overdiagnosis in screening group (19% overall)		40% overdiagnosis in screening group (30% overall)		Not recently screened group
	Entire screening group $N = 481$	Overdiagnosed cases $N = 119$	True cases $N = 362$	Overdiagnosed cases $N = 190$	True cases $N = 291$	$N = 150$
Breast surgery						
Mastectomy	76 (16%)	0 (0%)	76 (21%)	0 (0%)	76 (26%)	52 (35%)
Lumpectomy	405 (84%)	119 (100%)	286 (79%)	190 (100%)	215 (74%)	97 (65%)
Axillary surgery						
None	10 (2%)	2 (2%)	8 (2%)	4 (2%)	6 (2%)	6 (4%)
SN biopsy	380 (79%)	117 (98%)	263 (73%)	186 (98%)	194 (67%)	79 (53%)
Axillary dissection	91 (19%)	0 (0%)	91 (25%)	0 (0%)	91 (31%)	65 (43%)
Radiation therapy						
Post mastectomy	30 (39%)	0 (0%)	30 (39%)	0 (0%)	30 (39%)	30 (58%)
Post BCS	358 (88%)	105 (88%)	253 (88%)	168 (88%)	190 (88%)	88 (91%)
Adjuvant chemotherapy	180 (30%)	0 (0%)	180 (50%)	0 (0%)	180 (62%)	97 (65%)
Adjuvant endocrine Rx	413 (86%)	119 (100%)	294 (81%)	190 (100%)	223 (77%)	114 (77%)

patients today assume is true. However, 19% is large enough that we would not want to give up the benefit of screening. The risks of screening mammography include false positives, leading to unnecessary biopsies and overdiagnosis. Overdiagnosis is the most serious risk, primarily because it leads to overtreatment. Of course, in actual practice we cannot predict with certainty which cases are overdiagnosed. However, as we get better at predicting the biology of the cancer, we may be able to reduce the intensity of treatment for favorable cases that are likely to

be overdiagnosed. The recently reported TailorRx trial will allow us to avoid chemotherapy in a large group of patients.[12] We need similar trials to allow us to omit sentinel node biopsy and radiation therapy for indolent cases. Elder et al. believe that reduction in treatment intensity is a benefit of screening mammography. I believe that reducing the overtreatment caused by mammography is essential to improving the risk/benefit ratio for screening.

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