Understanding and managing breast cancer: *Quo Vadis?*

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Our understanding of breast cancer and how to manage it has undergone a sea change in the past decade. Untiring efforts of clinical and laboratory scientists have brought about these changes, which have increasingly been influenced by patient groups. My views about these changes are as follows.

Screening

By definition, a screening test should be simple, inexpensive, have a high sensitivity and help to reduce disease-related mortality. The screening test should also be highly specific if the intervention it suggests is surgery, which for breast cancer is usually disfiguring surgery. The presumed biological principle in screening is based on the conventional definition of neoplasia that 'cancer starts as a small mass of neoplastic cells and with time spreads to rest of the body—taking the life of the victim *if and* when these metastasis grow' (italics mine) Thus, if the tumour is removed *before* it spreads, cure should be expected. Unfortunately, current evidence from large Chinese and Russian trials suggests that despite high rates of compliance, breast self-examination is not effective in reducing mortality. While Gotzsche and Olsen[1] found no evidence of any benefit from screening mammography trials, a recent meta-analysis [2] which included 8 randomized, controlled trials of mammography and 2 evaluating breast self-examination found that the relative risk was 0.84 (95% CI: 0.77–0.91) and the number needed to screen to prevent one death from breast cancer after approximately 14 years of observation was 1224 (CI: 665-2564). Among women <50 years of age, the summary relative risk associated with mammography was 0.85 (CI: 0.73–0.99) and the number needed to screen to prevent one death from breast cancer after 14 years of observation was 1792 (CI:764–10 540). Clearly, it should be for the people to decide whether healthcare resources could be better spent.

For India, these analyses have come at the right time, because now we should have little qualms in saving all the money that would have been spent on screening mammography programmes. In any case, mammographic screening is nowhere near the ideal screening test—it is expensive, neither very sensitive nor specific for fatal cancers, and is perhaps less effective in reducing mortality. We need to await the results of an ongoing trial testing a pragmatic early detection strategy (I. Mittra, National Institutes of Health) and perhaps breast examination by *anganwadi* workers is the best way to reduce mortality from breast cancer.

The extremely modest benefit from screening, apart from causing general improvement of breast services, is disappointing and shakes long-held dogmas about the natural history of cancer. It may be pointing to a fundamental hidden biological clue.[3] Judah Folkman has elegantly shown that tumours cannot grow beyond 200 μm without stimulating their own blood supply. Thus, many primary tumours can exist in a state of dynamic equilibrium and suppress the growth of their own secondaries by anti-angiogenic paracrine secretions. Removal of the primary can provoke local angiogenesis from surgical trauma and release the secondaries from this inhibition and stimulate their growth. The paracrine secretion may be proportional to the tumour size until a critical level, when it can no longer inhibit the secondary growth effectively. This critical size may be different for individual tumours and could well be higher than the clinical threshold. Therefore, the term early cancer has no meaning, especially when by 60 years of age, every one of us harbours at least one of prostate, breast, thyroid or lung cancer in a subclinical (dormant) state, which is generally harmless.[4,5,6]

Effective treatment of cancer and reduction in mortality from cancer in general will be possible only if we follow a strategy based on these principles. Once a primary cancer can no longer effectively inhibit its secondaries, it could be safely removed and its anti-angiogenic effect replaced and

supplemented so that the secondaries remain suppressed. Removal of a primary cancer at an early stage when it is effectively suppressing its secondaries will only remove the inhibition of angiogenesis that will nullify any benefit from reduction of further metastasis. This mechanism could be the elusive answer to the puzzle of ineffective screening. We should stop talking about early cancer and start thinking about dormant/latent cancer and inappropriate early surgery. Perhaps the only way to cure some cancers is to learn ways to live comfortably with them.

Diagnosis

For a patient presenting with a breast lump, the most important service a specialist unit can provide is to exclude a breast cancer at the first visit. This can be done reliably using triple assessment—physical examination, imaging with mammography or ultrasonography, and microscopy—[which has traditionally relied upon high quality fine needle aspiration cytology (FNAC)]. A well performed ultrasonography is a useful and relatively cheap adjunct to clinical examination in the diagnosis of uncertain lumps, but cannot be used for screening. In experienced hands, concordant triple assessment has an extremely low false-negative rate. Core-cut biopsy is being used increasingly to conclusively give a preoperative histological diagnosis, especially when triple assessment is discordant, when major surgery such as mastectomy or neo-adjuvant chemotherapy is planned, or when it is important to ascertain the hormone receptor status in elderly frail women in whom surgery is not feasible. For lesions detected at screening, mammographically-guided FNAC or core-cut biopsy is being superseded by devices such as the Fisher Mammotest™ which uses digital mammograms in 2-directions enabling computation of the depth of penetration of the core-biopsy needle. And the simple core-biopsy needle is being replaced by vacuum-assisted devices such as the Mammotome™. With these devices, it is possible to obtain accurately directed high volume (1–2 cm^3) biopsies. In countries that already have established mammography services, and are flooded with increasing numbers of small cancers detected at screening with an uncertain natural history, these devices provide a possibility of a one-stop outpatient treatment when used along with small portable radiotherapy devices.[7]

MRI is increasingly being included in the diagnostic armamentarium of a typical western breast unit. MRI machines are becoming ubiquitous and the additional cost of a breast coil is very low. MRI is highly sensitive in detecting breast cancer but its specificity is low. In addition, in a large proportion of women, it may detect dormant cancers that may never have surfaced in the woman's lifetime.[8] The clinician is frequently forced to treat these 'occult' cancers with mastectomy when breast-conserving surgery would have been advised if MRI had not been performed. The patient may be falsely satisfied —'we caught it early'. An appropriate use of MRI is perhaps in screening women with a strong family history of breast cancer or those with known deleterious BRCA1 or BRCA2 gene mutations. However, the small number of these women and the associated anxiety has meant that its efficacy will never be evaluated in a randomized trial and it will only be used empirically.

Treatment

By the mid-1990s there was widespread belief that the extent of local treatment did not affect the long term outcome. This was probably already determined by the time the cancer was diagnosed. The belief was mainly prompted by the early Oxford overviews in which the small survival benefit from radiotherapy was nullified by its harm due to cardiac toxicity. The publication of two large Danish trials has shaken this 'proven' consensus. These trials involved women with larger breast tumours and/or many involved lymph nodes, who received adjuvant chemotherapy or tamoxifen.[9;10,11] Not surprisingly, there was a reduction in local recurrence rates but there was also an improvement in the overall 10-year survival rates (9%[9] and 10%[11]). The trials have been criticised because the surgery for these fairly large tumours was inadequate, thus accentuating the benefit by radiotherapy. However, the radiotherapy techniques in these two studies minimized the dose to the heart and included the internal mammary chain in the field. These factors could have contributed to the large improvement in survival. Another explanation for this large magnitude of the difference in survival rates could be a statistical quirk. Let us assume that radiotherapy does impart a small survival benefit. When several trials are conducted, the different magnitudes of effects seen are expected to follow a normal distribution. A

sufficiently large trial would be highly likely to detect this small difference whereas a small trial will rarely yield a positive result because of a type II error. The effect in a small trial will need to be larger than the real effect (just by chance) for it to be detected at all; consequently, small trials that are positive will usually be those which reveal a larger than real effect.

The long term results of the initial Guy's trials of conservative surgery which started in the 1960s have recently been published. They were the first to suggest that the extent of local treatment could affect survival. They found that radical surgery imparted a significant survival benefit[12] and this beneficial effect has actually been accentuated after 25 years of follow up.[13,14;14] In the first series, 374 women (>50 years) with T1, T2, N0 and N1 tumours were randomized to either a Halsted mastectomy or wide excision. Both groups were given 25–27 Gy to the gland fields and the wide excision group received an additional 35–38 Gy (inadequate by today's standards) to the breast. After 25 years, the local relapse was of course lower in the mastectomy group (26% *v.* 50%, $p<0.001$). The breast cancer mortality was also reduced (56% *v.* 63%, $p=0.02$). In a second trial, of 355 node-negative cases, the rates of local recurrence at 25 years were 18% *v.* 54% and there were significantly more breast cancer deaths in the latter group (57% *v.* 44%, $p=0.04$). These two trials, conducted before the widespread introduction of systemic adjuvant therapy, indicate the long term effects of inadequate primary treatment.

According to the latest Oxford overview,[15] radiotherapy in general reduced the relative risk of local recurrence by two-thirds (66% relative risk reduction, i.e. from 30% to 10%; a 20% absolute risk reduction) and reduced the risk of breast cancer death by about one-fifth of that reduction (i.e., 66/5=13.5% relative risk reduction=or 20/5=4% absolute risk reduction). Thus, the magnitude of the beneficial effect of radiotherapy is small and if the side-effects of radiotherapy can be completely avoided, it could improve the 20-year survival by about 2%–4%, the benefit mainly limited to those women who have a high risk of local recurrence. This small benefit is equivalent in magnitude to that obtained by adjuvant systemic chemotherapy in those above 50 years of age!

Nevertheless, properly delivered breast conserving therapy (BCT) is equivalent to mastectomy. In spite of this proof being available for more than a decade, the rates of mastectomy in various populations are still very high, and cannot be attributed to a late stage of disease. Local culture, surgeon's choice and patient preference, not necessarily in that order, all dictate which operation the patient undergoes. Even in developed countries such as USA, BCT rates can be very low. This also depends on how far the patient lives from the radiotherapy facility. Farther the patient lives, less is the likelihood that she will receive BCT and radiotherapy after breast conserving surgery (BCS). When the travel distance was <10 miles, 82% of patients received radiotherapy after BCS ; when it was 50–75 miles, 69% received it and when it was $\geq$100 miles, only 14% received it. These patients accounted for 39%, 22% and 14%, respectively, of those eligible for BCS and radiotherapy.[16] Many women in India are denied BCT only because they cannot live away from home near the radiotherapy facility to take the 6-week course of postoperative radiotherapy. When recurrence after (BCS) is analysed, it is found that it most commonly occurs near the scar of the primary tumour excision. This is true whether or not radiotherapy was given, suggesting that the multifocal/multicentric cancers in other quadrants of the breast probably remain dormant and are not clinically relevant. Based on this premise, we have pioneered [17] the use of intraoperative radiotherapy which is delivered as a single dose treatment targeted to the peri-tumoural tissues. In patients with a good prognosis breast cancer (these are becoming the majority), this could be the sole treatment and in the poor prognosis group, it would avoid any geographical miss, thus further reducing local recurrence. The results of pilot studies using one such device that uses soft X-rays (Intrabeam™) are encouraging and a randomized trial (TARGIT)[18,19] is under way in UK, USA and Australia and hopefully India. The Milan group is also testing the same approach,[20] using a mobile linear accelerator (NOVAC-7™) in a randomized trial (ELIOT). The completion of these trials is eagerly awaited. If proven effective, these novel approaches have the potential to save time, money and enable many more women to conserve their breasts.

Sentinel lymph node biopsy, using the blue dye and/or radioisotope to map out the first echelon of lymph nodes in the axilla is a novel way of reducing the morbidity of axillary surgery. Although it is still being

tested in randomised trials for those with infiltrating duct cancer, it is used frequently as a definitive treatment for pure DCIS (ductal carcinoma *in situ*) and even some very small cancers detected by screening . However, the much simpler and cheaper axillary sampling may give the same results, and a study comparing the efficacy of the two would be of great importance for Indian patients.

There seems to be substantial evidence that timing of surgery with respect to the menstrual cycle may have a significant impact on survival. However, randomized trials testing this hypothesis are lacking. We eagerly await the results of the Yorkshire group's (R. Sainsbury) prospective follow up study and the results of the randomized study from India (R. A. Badwe) which is testing the hypothesis that unopposed oestrogen at the time of intervention is detrimental to survival.

The concept of adjuvant (meaning in addition to surgery and/or radiotherapy) treatment for breast cancer is based on the premise that clinically diagnosed breast cancer has already spread beyond the breast. The likelihood of such a spread and consequently the relative benefit of treating these invisible 'micro-metastasis' with systemic treatment, either hormonal or cytotoxic chemotherapy, depends on the stage and perhaps the aggressiveness of the primary tumour.

According to the latest version of the Oxford overview, adjuvant chemotherapy reduces mortality by 27% in those <50 years of age and by 11% in those >50 years. However, the absolute risks must be balanced with the side-effects of treatment. This typically produces an absolute improvement of about 7%–11% in 10-year survival for women below 50 years of age at presentation with early breast cancer, and of about 2%–3% for those 50–69 years of age (unless their prognosis is likely to be extremely good even without such treatment). Tamoxifen is of benefit only in oestrogen receptor-positive tumours. Oophorectomy in pre-menopausal women is at least as beneficial as tamoxifen. The benefit of hormone treatment is at least as much as that of chemotherapy although the combination would increase the benefit. An excellent software has now been developed by Peter Ravdin that can calculate the absolute benefit of taking various types of adjuvant therapies for an individual patient.

The controversy whether chemotherapy works only indirectly (chemical castration causing amenorrhoea) is not completely resolved and currently many centres treat those young women who do not develop amenorrhoea after chemotherapy, with temporary chemical castration by goserelin (Zoladex™).

Although anastrazole (Arimidex™), the aromatase inhibitor has been clearly shown in the largest randomized trial (ATAC) to be better than either tamoxifen or a combination for disease-free survival, we need to await the results of overall survival and mature toxicity profiles before it can substitute tamoxifen[21-23].

Thankfully, high dose chemotherapy and bone marrow transplant, the treatment prompted by its success in leukaemias, should be a thing of the past. Tens of thousands of women and billions of American dollars were spent on these treatments to 'fight' the war against the cancer. Alas, the biology of the disease is so elusive that even after the last cancer cell is supposedly killed, the cancer still kills the patient.

Quo vadis?

That brings us to new models of disease that are urgently needed to explain the numerous paradoxical phenomena in the natural history of breast cancer. To name a few: why does the hazard of recurrence after breast cancer diagnosis peak at about 2–3 years, irrespective of the stage of the disease (the stage only affects the amplitude of the hazard peak, not its timing)? Why do breast cancer survivors keep dying from the disease 30 years after diagnosis? How do the cancer cells survive in this quiescent period? Why does adjuvant therapy or high dose chemotherapy not work as much as it is expected? And why does the same disease behave so differently in different individuals?

These questions remain to be answered. And new models based on new mathematics of chaos and of non-linear dynamics[24], new knowledge of molecular mechanisms, angiogenic or even psychoneurohumoural controls would hopefully shed light.

While we continue to push the limits of our ignorance in trying to solve the mysteries of this relatively common disease that can have devastating effects on the individual and her family, I wish to stress an important point about breast cancer--that it is a rare cause of death even in the West, responsible for only 2%–3% of all deaths among women. The figure is likely to be 5–10

times less in India. This should be taken in perspective of the deaths and misery that could be prevented by tobacco eradication. Tobacco is responsible for between 10-20% of all deaths (it is responsible for 50% of deaths among tobacco users which form about 30-50% of the population) and 40- 50% of premature deaths, taking away on an average 23 years of life, in addition to time, money, trees and healthcare resource.

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