The Roles of the Learned Societies in Improving Quality of Life in the context of Globalisation

Michael Baum MB, FRCS, ChM, MD (hc), FRCR (hc)

The globalisation of commerce, the development of social network information technology, and relative ease of travel, have matured the concept of the global village. In turn, the duty of care, from those countries that are resource-rich to those countries that are resource-poor, becomes an ethical imperative. Hence, if we love our neighbour as ourselves, then we cannot stand by and watch them suffer, nor must we squander scarce resources for tiny incremental improvements in health care for the rich, whilst the poor of this world die prematurely from easily preventable or treatable disease. To put these high minded ambitions into practice, on a grand scale, is a mighty challenge. However, one can begin to appreciate the principals involved using the example of one disease that is responsible for the premature deaths of thousands of women round the world every day; that is carcinoma of the breast.

There are only two meaningful outcome measures in the evaluation of health care; simply put, they are length of life (LOL) and quality of life (QOL). All other outcomes are surrogate and, however compelling the results of screening, blood tests, and medical images might be, they may not translate into improvements in LOL and QOL.1 This is never truer than in the discussion of cancer care. LOL is, of course, easy to measure but even cancer ‘survival’ statistics can be misleading unless they translate into mortality reduction. ‘Survival’, represents LOL from point of diagnosis, whilst mortality counts the number of age-matched individuals dying from the disease on a year-by-year basis. Merely frame shifting the point of diagnosis ‘to the left’ canartifactually extend survival without affecting mortality. QOL is not as simple to measure; however, psychometric instruments for this purpose have been available since the mid-1970s and are continually refined and validated.2,3

To illustrate the important generic issues mentioned above, one can discuss breast cancer prevention, screening, surgery, systemic therapy, and radiotherapy. The intention being to concentrate on real advances that are transferable to resource poor parts of the world. This can be achieved while learning from the extravagant errors made by some of the wealthiest nations of the world, who have demonstrated that wealth and wisdom do not always go hand in hand.

Outcome measures

There are only two meaningful outcome measures in the evaluation of health care; simply put, they are length of life (LOL) and quality of life (QOL). All other outcomes are surrogate and, however compelling the results of screening, blood tests, and medical images might be, they may not translate into improvements in LOL and QOL.1 This is never truer than in the discussion of cancer care. LOL is, of course, easy to measure but even cancer ‘survival’ statistics can be misleading unless they translate into mortality reduction. ‘Survival’, represents LOL from point of diagnosis, whilst mortality counts the number of age-matched individuals dying from the disease on a year-by-year basis. Merely frame shifting the point of diagnosis ‘to the left’ can artifactually extend survival without affecting mortality. QOL is not as simple to measure; however, psychometric instruments for this purpose have been available since the mid-1970s and are continually refined and validated.2,3

Prevention

It is an old cliché that prevention is better than cure. The incidence of breast cancer shows an almost linear correlation with the GDP of nations. As such, maybe the resource rich nations of the world have something to learn from the resource poor. Of course that is a gross over simplification; cancers of most types increase in incidence with age, and expectation of life is directly correlated with the wealth of nations. However, if one recalculates these numbers with adjustment for age, the resource poor sections of the globe still have a lower incidence of the disease. The best advice, therefore, for resource poor parts of the world, is not to ape the lifestyle choices of the women living in northern Europe or North America.3
Screening

A point has been reached where the majority of women, in the resource-rich parts of the world, are breast cancer aware and present with a disease that has the potential for cure. It is likely that this, in part, might have contributed to the welcome fall in mortality we have experienced over the last 20 years.2 Breast cancer ‘awareness’ is not high technology, but dependant on public health education and resources; focus on this alone is likely to generate greater dividends than screening of any kind. If the resource-poor nations of the world are to learn anything from our mistakes of the past, then they need to recognize the folly of the widespread adoption of mammographic screening in Europe and North America. Screening has a great future behind it!

Screening illustrates our reliance on surrogate endpoints and the injustice of squandering scarce resources on interventions of trivial incremental gain, to the detriment of the rest of the world. ‘Catch it early’ is the mantra and ‘save a life and save a breast’ is the refrain. ‘Catch it early’ means detecting the cancer at a pre-clinical stage. That is a surrogate end point that fails to translate into improving LOL and QOL. Screening does not save lives and, paradoxically, increases the mastectomy rate in screened populations. There is a rich bibliography of recent publications that support this argument.5–11

Surgery

In the 1960s, radical mastectomy was the treatment of choice for breast cancer, and pathological clearance was used as the surrogate marker for success. Yet patients continued to die of metastatic disease in spite of clear margins. A revolutionary conceptual model of the disease was elaborated in the 1970s that led to a change of therapeutic approaches.12 Instead of looking at the disease as an anatomical challenge (that might be cured by surgery alone); it was considered a biological challenge with outcomes predetermined on the extent of occult metastatic disease present at the time of diagnosis. This lead to a series of trials, with breast conserving surgery as a challenge to radical mastectomy, with the objective of improving QOL.

After decades of fierce debate and clinical trials, a consensus has been reached that breast conserving surgery (BCS), whenever technically feasible, should be the default treatment.13 This should be welcomed by resource-poor nations because BCS is quicker and requires fewer days of hospitalization than a mastectomy with or without reconstruction, but with two important caveats.

First, the onus is on the woman herself to present when her tumour is small enough for BCS. As stated above, that is dependent on public health education. Secondly, BCS is only a safe alternative if accompanied by 3 to 6 weeks radical radiotherapy; this is a labour intense, high-technology, intervention that also implies that the patient has easy access to a radiotherapy centre.

Adjuvant systemic therapy

BCS, plus radiotherapy, may indeed be non-inferior to radical mastectomy and thus improve QOL, but that alone does not improve LOL. To deal with that problem, one needs to look elsewhere. The paradigm shift in our contemporary understanding of breast cancer, posited the concept that the disease had to be considered a systemic disorder at the point of diagnosis.12 Should that be the case, then to improve LOL, some form of adjuvant systemic therapy (AST) must be indicated. Randomised controlled trials, on AST using chemotherapeutic regimens and endocrine agents, started in the mid-1970s and continually refined to this day, have confirmed their potential to improve LOL. The 30–40% reduction in breast cancer mortality enjoyed in Europe, since the mid-1980s, has recently been attributed to the introduction of AST with no contribution from screening, using the World Health Organization (WHO) database.6 Complex chemotherapy regimens are costly and difficult to deliver; yet tamoxifen, a drug that has been credited with 60% of the improvement in breast cancer mortality, is now available as a cheap generic compound.14

Unfortunately, endocrine agents, such as tamoxifen, are only of value in oestrogen receptor positive (ER+) cases. The onus is on the resource-rich parts of the world to develop less costly, less complex, chemotherapy regimens for the developing parts of the world. This should be instead of squandering increasing quantities of their GDP on miniscule incremental improvements that offer at best a few more months of ‘progression free survival’; another bogus surrogate for LOL, as exemplified by the recent scandal with Avastin.15

Radiotherapy

There is inadequacy in the provision of radiotherapy centres for women around the world. In the poorest countries in the world, women with early breast cancer cannot be offered BCS because of this. This is also evident in countries with large rural areas and difficult access to the nearest major cities. A golden age, when all women in the world suffering with breast cancer, have easy access to post operative radiotherapy is highly unlikely. To this end, we need some original thinking, ‘outside the box’, to offer a solution. If the woman cannot get to the radiotherapy unit, then the radiotherapy unit must come to the woman.

One way, that may answer the problem, is the employment of a simple mobile radiotherapy unit. This unit (INTRABEAM) can provide a one shot intra-operative radiotherapy (IORT), targeting the area around the primary tumour, that has been accepted as being equivalent to 5 to 7 weeks of conventional external beam treatment in selected cases. The rationale for targeting the area around the primary tumour comes from clinical correlation of whole organ analysis of mastectomy specimens. It has been well demonstrated that the female breast frequently harbours more than one tumour and these are found if one looks hard enough. Autopsy studies have demonstrated such tumours in up to 20% of women (with a median age of 39);16 this is supported in mastectomy specimens.17 However, their widespread, three-dimensional, distribution does not correspond to the location of recurrences after breast conserving surgery.18,19 Most commonly (about 90%), recurrence occurs in the area around the scar of primary excision (index quadrant). Hence, it follows that radiotherapy, after surgical excision, should be targeted to the area around the primary tumour (i.e. the tumour bed).

Conventional external beam radiotherapy is very successful and reduces the rate of local recurrence by 2/3. But, this means it fails in 1/3 of cases. This could be because of intrinsic resistance of any residual cancer cells, or due to the radiotherapy dose ‘geographically’ missing the target tissues or ‘temporally’ missing the window of optimal opportunity. It is interesting that the proportional reduction of the risk does not change with increasing size of excision. Hence, just...
excising the cancer, with a larger margin, will not eliminate the risk. As IORT is delivered immediately after surgery, it may avoid missing the target either geographically and temporally.

In 1998, University College London, pioneered the approach of targeted intraoperative radiotherapy (TARGIT).20,21 With this technique, using the Intrabeam™ system, a single fraction of 20Gy is delivered to the surface of the tumour bed, using a spherical applicator, from within the breast. The surgeon ‘wraps’ (or conforms) the pliable tumour bed around the applicator, ensuring close apposition of the target tissue to the radiotherapy source. The technique needs to be meticulous but is relatively straightforward. So far, over 4,000 patients have been treated worldwide. Although the approach of concentrating on the tumour bed is not new, modern technology has allowed it to be used with relative ease in a routine operating theatre, and with a potential for significant economic saving.

After successful completion of a pilot study,22 the TARGIT A trial was launched in March 2000. In this trial, women who were older than 45 years, and those who did not face a high risk of developing recurrent or multiple cancers in the breast, were included.23 In fact, these women form the majority of breast cancer patients. The randomly allocated treatment that followed wide excision of the cancer (lumpectomy) was either targeted IORT, or the usual 3 to 6 week course of external beam radiotherapy. The aim of the trial was modest: to investigate if the two treatments were equivalent. But, if proven, the prize was great; women could then avoid the 30–40 visits to the radiotherapy centre and still conserve their breast. The results of the TARGIT A trial, in terms of safety, efficacy, and patient satisfaction, have now been published.24,25 Furthermore, evidence in support of its adoption for carefully selected cases, emerges from a number of consensus statements that include one from the American Society of Breast Cancer Surgeons, and one from the biennial European St Gallen conference.24,25

The most recent and, in many ways, most exciting example of the transfer of appropriate technology, has been the establishment of the first unit in Thailand for delivering IORT after breast conserving surgery, at the Queen Sikirit breast cancer centre in Bangkok. One can now witness the true meaning of globalization at its best. The invention of a miniature electron generator/accelerator in Boston MA, incorporated into a mobile X-ray treatment unit by Carl Zeiss in Germany, pioneered for the single dose treatment of breast cancer by a team based at University College London, and tested in a multinational clinical trial in 11 countries. Thai women, who live too far from a radiotherapy centre, can now enjoy the benefits of BCS, with a stay of one day rather than six weeks in the big city. The future vision is to provide one of these mobile units on a railway train to travel up and down the country, acting as a mobile education and treatment centre. The fulfillment of this vision now depends on political will, rather than technology transfer.

That aside, we can take comfort from the fact that globalization of scientific endeavour can improve both LOL and QOL, for at least one common cancer type, anywhere in the world. No doubt others will follow the path beaten by breast cancer pioneers. All that the masters of our universe have to do to achieve this ambition is to remember the biblical injunction: “Thou shalt love thy neighbour as thyself.”

Ethical approval
No ethical approval required for this study.

Conflict of interest
The author declares a previous relationship with Carl Zeiss who have provided consultancy fees, honoraria, and travel expenses.

Author contribution
Single author manuscript.

Funding
No funding source declared by author.

References
1. Momoh K, R. Surrogates under scrutiny. BMJ. 2011;343:399–401.
2. Priefert TJ, Baum M. Evaluation of quality of life in patients receiving treatment for advanced breast cancer. Lancet. 1976;1(7985):899–901.
3. Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. J Exp Clin Cancer Res. 2008;27:32.
4. Dhillon PK, Yeole BB, Dikshit R, Kulkarni AP, Bray F. Trends in breast, ovarian and cervical cancer incidence in Mumbai, India over a 30-year period, 1976–2005: an age-period-cohort analysis. Br J Cancer. 2011;105(5):723–30.
5. Autier P, Boniol M, Gawn A, Vatten LJ. Breast cancer mortality in neighbouring European countries, with different levels of screening but similar access to treatment: trend analysis of WMH mortality database. BMJ. 2011;343:d441.
6. Jørgensen KJ, Gøtzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. BMJ. 2009;339:b2587.
7. Welch GH. Black WC. Overdiagnosis in cancer. J Natl Cancer Inst. 2016;108:605–13.
8. Welch HG. Screening mammography – a long run for a short slide? N Engl J Med. 2010;363(13):1276–8.
9. McPherson K. Should we screen for breast cancer? BMJ. 2010;340:233–5.
10. US Preventive Services Task Force. Screening for breast cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2009;151(10):716–26.
11. Gøtzsche PC, Nielsen M. Screening for breast cancer with mammography. Cochrane Database Syst Rev. 2009:III:1-4 (CD001877).
12. Baumb M. Biological considerations in the management of early carcinomas of the breast and their role in the selection of therapy. Ann R Coll Surg Engl. 1980;62(1):35–8.
13. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233–41.
14. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687–717.
15. Jones A, Ellis P. Potential withdrawal of bevacizumab for the treatment of breast cancer. BMJ. 2011;343:d4946.
16. Nielsen M, Thomas JL, Prindahl S, Dyrberg U, Andersen JA. Breast cancer and atypia among young and middle-aged women: a study of 110 medicolegal autopsies. Br J Cancer. 1987;56(6):814–19.
17. Holland R, Veling SH, Mhravan M, Hendrikx JH. Histologic multifocality of T1, T2–T3 breast carcinomas. Implications for clinical trials of breast-conserving surgery. Cancer. 1985;56(5):979–80.
18. Vaidya JS, Vyas JJ, Chinsky RF, Merchant NM, Sharma OP, Mittra I. Multicentricity and its influence on conservative breast cancer treatment strategy. Hong Kong International Cancer Congress. 1995:Abstract 44.4.
19. Baumb M, Vaidya JS, Mittra I. Multicentricity and recurrence of breast cancer. Lancet. 1997;349(9046):208.
20. Vaidya JS: A novel approach for local treatment of early breast cancer. PhD Thesis, University of London. 2001. [online]. http://www.bunde.ac.uk/~java/papiers/thesis.htm (Accessed: 7 August 2012).
21. Vaidya JS, Baumb M, Tobias JS, et al. Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. Ann Oncol. 2001;12(8):1075–1086.
22. Vaidya JS, Baumb M, Tobias JS, Morgan S, D’Souza D. The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer. Eur J Surg Oncol. 2002;28(4):447–54.
23. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet. 2010;376(9735):91–102.
24. The American Society of Breast Surgeons: Consensus Statement for Accelerated Partial Breast Irradiation. 2008 [online] https://www.breastsurgeons.org/statements/PDF_Statements/APBI_statement_revised_100708.pdf (Accessed: 7 August 2012).
25. Goldberg I, Wood WC, Coades AS, et al. Strategies for subgroups – dealing with the divers- ity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. Ann Oncol. 2011;22(8):1736–1747.

Open Access
This article is published Open Access at annalsjournal.com. It is distributed under the AMS terms and conditions, which permits unrestricted non commercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.

www.annalsjournal.com
Annals of Medicine and Surgery 2012; 1(1): 16–18