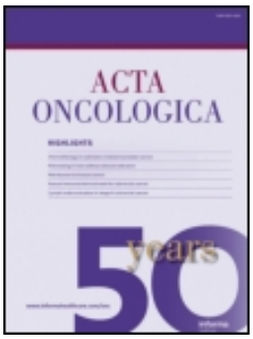

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EDITORIAL

DBCG: The Danish Breast Cancer Cooperative Group – a 30-year struggle for better breast cancer treatment in Denmark

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The current issue of Acta Oncologica is devoted to the commemoration of DBCG, the Danish Breast Cancer Cooperative Group's 30-year anniversary. The issue therefore reflects the outcome of a long-term organisational and scientific effort towards improving the treatment of breast cancer in Denmark. DBCG has served as a paragon for the professional organisation of cancer treatment in both Denmark and other Nordic countries and the anniversary therefore gives us a good reason to present some of the outcomes, and to reflect on the most recent three decades of cancer research and treatment.

It is characteristic that in these years we are going through a wave of fashion which focus on the so-called "retro style", and what can be more relevant than a reflection on the cancer treatment in the 1970's and the consequent spin-off.

Imagine therefore the situation in the 1970's. Cancer treatment, and especially breast cancer treatment had for a long time followed the same track which was formulated by Halsted with his hypothesis that breast cancer is a locoregional disease which spreads from its origin, and the way to cure it must therefore be an eradication of the locoregional disease [1]. This had initially led to the extensive surgical approaches which in turn were taken over by a less mutilating and simpler mastectomy supplemented with postoperative radiotherapy. The latter most frequently given with ortovoltage treatment according to the McWhirter technique [2]. The few clinical trials in breast cancer were devoted to reduction of extent of the surgical procedure by supplementing it with radiotherapy, and one of the most influential trials in that aspect was the study by Kaae, Dahl Iversen and Johansen which demonstrated that extensive surgery was not necessary. This study is updated with a 50-year follow-up and included in the current issue [3]. The organised use of adjuvant systemic therapy was in its early days and initially mainly in a form of single drug treatment such as cyclophosphamide as it was supplied in the Norwegian trials by Nissen-Meyer [4]. But then a dramatic change occurred in the 1970's. The development of medical oncology took off and in breast cancer the initial results of multidrug adjuvant therapy to high-risk breast cancer, which came at almost the same time from the American and Italian groups, together with an identification of patients as being in high risk based on the number of tumour positive lymph nodes [5,6]. This put a pressure on the oncological community and in reality changed the paradigm for the treatment of breast cancer into the more systemic approach saying that breast cancer is to a large extent a systemic disease which has disseminated at the time of diagnosis. Thus the treatment must therefore be directed towards the systemic spread of the disease and consequently less focus should be given to the locoregional treatment [7]. The interest and change of focus were therefore very much in the dispute in the mid-seventies and also caused a commotion in the organisation of non-surgical oncology. Whereas this in most parts of the world resulted in the development and strengthening of medical oncology as a specific new speciality did we in Scandinavia and parts of northern Europe maintain another more

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integrated approach. This was to a large extent due to the visionary attitude by two individuals, Jerzy Einhorn at Radiumhemmet who had foreseen the need for an organisational change but also was strongly in favour of keeping that within a single speciality rather than dividing the non-surgical oncology into several minor disciplines which probably might interact to a lesser extent [8]. The same visionary approach was formulated by Michael Peckham in UK and consequently the Scandinavian and northern European oncology developed more into a direction of clinical oncology rather than into different disciplines [9]. This did not happen without a struggle between various opinions but has nevertheless resulted in the establishment of clinical oncology as a specific speciality which in Denmark is taking care of both radiotherapy and medical oncology in adult patients with solid malignancies.

It was on this turbulent basis the formation of DBCG took place. In Denmark there was at the end of the 1970's a strong interest in a new organisation of cancer treatment both based on the influence from the systemic drug therapy as well as a change in radiotherapy due to the increasing use of high-voltage linear accelerators and the subsequent fading out of traditional ortovoltage treatment which in turn resulted in a centralisation of the centres for non-surgical oncology. The same need for structural collaboration was therefore formulated both from the surgical and non-surgical partners resulting in formation of a number of multidisciplinary groups such as DBCG, the head and neck oncology group, DAHANCA, a testis cancer group, DATECA, and the Hodgkin and lymphoma group, LYFA and LYGRA. These were later followed by other groups but the initial strong and active were DBCG and DAHANCA probably because they managed to establish an infrastructure on a multidisciplinary speciality level and with associated research and, most importantly, funding. Both of these groups have therefore developed and survived and have had a substantial national and international impact.

The detailed history and development of DBCG is described in the following papers [10–12], but in retrospect a few issues are noteworthy to bring forward.

DBCG has managed and organised the treatment of breast cancer in Denmark and thereby change both surgical, pathoanatomical, and clinical oncological practice. By instituting guidelines at an early stage and at the same time establishing a database with reporting of patient, tumour, and therapeutic data an early overview of the status and treatment of breast cancer in Denmark was established, and as a consequence the organisation of the initial diagnostic procedures and surgical handling of the patients was modified. DBCG was thus one of the first places where a more formal quality assurance procedure was formulated and consequently resulting in a reorganisation of (especially) the surgical handling of the disease. These criteria were, however, rather modest because it was more in focus that they should be achievable for everyone, rather than being stringent guidelines. The latter probably also because the importance of adapting more stringent guidelines was not really understood at the early stage. It is, however, characteristic that e.g. the requirement for number of lymph nodes removed in the axilla was considered less in Denmark than it was in other places with established guidelines such as Sweden. It is first in the recent years that a more international standard has developed within the DBCG.

DBCG developed an early national translational research and biobank structure The organisational aspect of DBCG was also the platform for the development of a structure for hormone receptor analysis which took place during the 1970's and 80's. The use of antioestrogen treatment with Tamoxifen was in fact instituted prior to the identification of the hormone receptor status in the tumour. The latter was based on intensive research in institutes collaborating with DBCG and during a number of initial trials both the methodology and usefulness of hormone receptor assays were established [13]. Thus, in the mid-seventies an organisational structure was set up by which all patients who underwent surgical intervention for breast cancer had their fresh-frozen specimens collected at three dedicated laboratories to perform the hormone receptor analysis. In reality this created a structure for collection of tumour tissue at a time when this was not in fashion, and subsequently the storage of the remaining tissue formed the basis for the DBCG tumour tissue bank. The research linked with development of the receptor assay was also subjected to quality procedures, and the DBCG research effort was of paramount importance for establishing of international standardisation of these assays and their implementation [14]. Unfortunately, the technology developed further and as indicated elsewhere in the current issue the initial biochemical charcoal extraction assay was exchanged with immunohistochemistry which could be done routinely on the ordinary specimens and therefore the initial collection of fresh tissue and the platform for translational research and biobanking regretfully vanished almost on date in August 1992, and subsequently the collection of biological material from the tumours and patients has been on a less

organised level. Thus another example of how DBCG has been able to react to immediate needs, but on the other hand has not been very visionary in its overall approach, and now we are in the process of re-establish the structure in order to adapt to modern individualised targeted therapy.

The scientific impact of DBCG has in a similar fashion mainly been a product the outcome of the protocols implemented as a part of the various programmes, especially the three first programmes initiated in 1977, 1982, and 1989, but again some of the data are not so much results of planned strategies as it is of scientific serendipity. It is therefore characteristic that the probably most known and influential international contribution from DBCG, the clinical trials of postmastectomy radiotherapy from the DBCG 82b&c protocols [15–18] were not initiated with the aim to evaluate the benefit of radiotherapy but should be more seen in the light of attempts to avoid radiotherapy by intensifying the systemic treatment. Thus, the trial was initially designed in the light of the systemic paradigm under the assumption that if sufficient systemic treatment was given there would be no need for adjuvant post-operative radiotherapy. It took therefore a while before the trial was finally analysed and in fact when the first data was emerging the initial endpoint of disease specific survival was changed to overall survival because some members of the group did not believe in the results and an additional quality assurance procedure was set up to check the outcome. So the benefit of postmastectomy irradiation which developed through the subsequent analysis of the studies was to some extent an unexpected surprise and should now be seen in the emerging light of the current hypothesis for the development of spread of breast cancer, the so called Hellman spectrum theory [19]. Nevertheless, the outcome of this trial has had a very substantial international impact and a consequential promotional effect of "the Danish trials". The publications from the postmastectomy studies is among the most cited breast cancer trials in the world and has subsequently been cited in more than 100 editorials worldwide. As a natural consequence the data has also influenced the outcome of the EBCTCG overviews (among other reasons due to the large number of patients in the study) and has in turn caused the indication for postmastectomy radiotherapy in high-risk breast cancer patients to be part of the current international recommendations and guidelines. The 82-trial is also interesting from the point of view that it includes another element of scientific serendipity, namely the fact that the applied radiotherapy technique was so that it did not involve the heart to any significant extent [20,21]. That technique was instituted at a time where our knowledge about the importance and dangers of cardiac irradiation was not known, and whereas many patients regretfully have suffered from late radiation-induced cardiac problems this has not been the case in the DBCG series. This may in turn probably be the reason why we have obtained a significant survival benefit in our irradiated patients: they have simply not suffered from the adverse effect of irradiation induced cardiac morbidity which is seen in other series [22]. The Danish patients are therefore also now part of a large international study evaluating this side effect (RACE) [23].

But not all trees grow into heaven and not all radiotherapy result in successful outcome. With the introduction of a standardised high-voltage radiotherapy in the initial 1977 programme we also introduced the use of hypofractionation (which was given to critically involved tissue of the axilla and thorax). Regretfully, this took place without a controlled clinical trial, and it was first at subsequent follow-up that an excess radiation-induced morbidity was noted [24]. Although this fractionation practice was abandoned in the early 80's a number of patients suffered from unnecessary side effects [25–28]. The scientific spin-off was an intense research into the mechanisms and outcome of hypofractionation and most of all clinical knowledge related to current fractionation sensitivity, alpha-beta ratios and other information which today creates the foundation of our understanding and radiotherapy fractionation and the underlying biological mechanisms has in fact been derived from this negative experience [29–32]. The lesson from this is a warning against introducing new treatment strategies without having a comparative platform, preferably in the form of a controlled clinical trial.

The political impact of DBCG has been less successful. Whereas DBCG has been instrumental in securing a continuous improvement of the treatment of breast cancer the overall political success related to reduction of breast cancer death has been at a lower level. This is especially because DBCG despite strong advocacy and argumentation has been unable to persuade the health authorities about the need of a nationwide screening for breast cancer. Breast cancer in Denmark is therefore considerably more advanced at the time of diagnosis (e.g. when compared to Sweden), and since the stage of disease is the most crucial factor related to outcome the survival of the breast cancer in Denmark is still inferior to countries where screening has been

implemented for a long time [33]. Nationwide breast cancer screening has now been implemented in Denmark as in the remaining part of EU per January 2008, but it is a sad example of how professional advice has not been able to penetrate to a decision making level despite strong supportive research and outcomes worldwide and especially in our neighbouring countries.

DBCG has extended the international collaboration. The most recent DBCG programmes have not included large-scale national clinical trials but have more been focused towards being a collaborator in large international studies such as the BIG 1-98 [34–36]. As it appears from the overview in the current issue DBCG has contributed substantially to such international efforts, but again it has become obvious that there maintain a need for a national collaboration, rather than individual Danish departments becomes small partners in international protocols [11]. The future time period is therefore likely to see the return of national protocols such as the planned REAL and READ projects as well as new attempts to reduce the burden of locoregional treatment and especially radiotherapy in the form of partial breast irradiation to low-risk patients [11,21,37].

Translational research aiming for a better understanding of the biological nature of breast cancer and subsequently attempts to target the treatment accordingly have been more obvious and successfully applied in breast cancer treatment than in any other site. Most prominent, of course, is the modification of the hormonal influence, and continuous research and trials directed towards using this target is ongoing [38]. This also requests more detailed knowledge about the biological nature of the disease and thereby access to the relevant tissue for identification. The need for a renewed collection of biological material in the form of biobanking and subsequent diagnostic procedures is therefore underway in DBCG, and large-scale national and local projects have recently attracted substantial funding for research. Examples are the interest towards identifying new targets such as TOP2A which may serve both as a prognostic and predictive parameter [39,40]; the use of TMA for better biological understanding of indications for radiotherapy [41,42], development of prognostic genetic profiling [43], studies of the hereditary genes [44], and further utilisation of the DBCG database and biobank material in an attempt to link clinical outcome with the tumours biological properties [45–48]. There is no doubt that a more intense biological assessment of the cancer in question is needed and will be part of future therapeutic indications and strategy and DBCG's structure is well set up for implementing of such activities. In a similar fashion a more recent focus on avoiding axillary surgery has also been successfully implemented with adaption of the sentinel lymph node biopsy techniques [49–51]. Again this is an example of how the professional structure of DBCG is successful in setting the standards and securing the necessary accreditation of the new procedures.

DBCG has set the standard for clinical cancer care in Denmark. The structure of handling of cancer patients in Denmark has undergone substantial changes recently with implementation of two national cancer plans and a subsequent extension with so-called treatment packages which should optimise the therapy and minimise delays. In the development of this approach where so-called DMCGs (Danish Multidisciplinary Cancer Groups) have become the fundament it is noteworthy that the whole basis of this structure of multidisciplinary professional groups developing guidelines for databases, translational research, platforms and other infrastructure has been built using the DBCG concept as the paragon for the future national cancer treatment infrastructure [52]. Thus, as we celebrate the 30-year anniversary of DBCG we can also conclude that it has overall been a long interesting and frequently unexpected journey into the jungle of improved health care but that it must be considered a successful event as seen by the adaption of this approach into the entire Danish system of management of cancer. Thus, the DBCG concept has been broadened out and proliferated so there are now more than 20 Danish multidisciplinary cancer groups built on the same principles and hopefully resulting in a similar success story.

DBCG has secured at better survival for breast cancer patients in Denmark. As it will appear from the subsequent papers in this issue [10,12], the contributions from DBCG has most likely resulted in a improved management of the diagnosis and treatment of the disease, which in turn has improved the overall survival rate. Although there is no foolproof evidence that these two conditions are linked it is obvious to consider the survival benefit to be caused by the influence of DBCG's strategic developed programmes and protocols. Furthermore this scenario is expected to be even better through the, regretfully delayed, additional benefit of the just implemented national screening programme.

DBCG has become full-grown. The 30-year of DBCG activities also mark the ending of the first generation of the groups leaders and organisers as the past leadership has or is about to reach professional retirement and leave it to a new generation to bring the torch forward. Thus, the troika of Mogens Blichert-Toft, Henning Mouridsen and Marie Overgaard have with great skills managed to lead the integration and development of surgery, medical oncology and radiotherapy into a well balanced multidisciplinary effort. This has not only resulted in an improvement of breast cancer treatment in Denmark but also in a substantial contribution to our global knowledge of how to deal with this challenging disease. Thus, the concept of DBCG with its idea of multidisciplinary handling of breast cancer has matured and succeeded.

Congratulations!

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