CAMBRIDGE

Cambridge University Press
0521496322 - Medical Therapy of Breast Cancer
Edited by Zenon Rayter and Janine Mansi
Excerpt
More information

1

History of breast cancer therapy

Zenon Rayter
Bristol Royal Infirmary, Bristol, UK

History of surgery for breast cancer

Introduction

Breast cancer is an ancient disease and was described by the Egyptians 3000 years before Christ. Subsequently various articles about breast cancer and its treatment were written by Greek and Roman physicians. Surgery is the oldest method of treating breast cancer with different operations described which sometimes reflected beliefs held about its causes and natural history. However, a variety of 'medical' therapies have also been described, especially in the Middle Ages, which to the modern observer were more akin to witchcraft than the application of scientific knowledge to the treatment of the disease. Changing fashions in the treatment of breast cancer have reflected not only changes in beliefs regarding its pathogenesis but also a growth in knowledge about the disease as well as advances in science and technology. Thus four periods can be discerned in the evolution of treatment over the centuries. The first period could be described as the Empiric era of the pre-Galen period. Subsequently, breast cancer was regarded as a systemic disease and this characterized the Pessimistic period. By the eighteenth century, breast cancer was thought to be a local disease leading to the Optimistic era in which it was believed that larger operations than performed previously could eradicate the disease. By the twentieth century, knowledge about the biology of breast cancer had started to grow which led to a realization that breast cancer was a more complex disease than previously had been supposed and led to the establishment of the Realistic era in which we now find ourselves. The twentieth century also saw the introduction of radiotherapy in the treatment of breast cancer, and medical therapy began to emerge from its primitive treatment concepts of the Dark Ages to emerge as a major new therapeutic tool. Philosophically, the emergence of medical therapy was conceptually different to that of surgery (apart from surgical endocrine manipulation) in that it was a systemic therapy as opposed to a local therapy. The emergence of these non-surgical modes of

© Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
0521496322 - Medical Therapy of Breast Cancer
Edited by Zenon Rayter and Janine Mansi
Excerpt
More information

treatment has been pivotal to the way that surgery has changed in the management of breast cancer over the last 50 years.

The empiric period

The earliest record of breast cancer comes from the Edwin Smith surgical papyrus which dates from Egyptian times (3000–2500 BC) and describes eight cases of tumours or ulcers of the breast, the writer admitting that there was no treatment, although one case was treated by cauterization with a fire stick. Writings dating from 2000 BC on cuneiform tablets from Assyria only mention the occurrence of breast cancer, but those from India mention the treatment of breast cancers with surgical excision, cautery and arsenic compounds. The first recorded 'cure' is credited by Herodotus (484–425 BC) to Democedes, a Persian physician living in Greece who treated the wife of King Darius. The most famous of Greek physicians, Hippocrates (460–370 BC) mentioned breast cancer only twice and advised no treatment. The early Romans performed extensive surgery for cancer of the breast, including removal of the pectoral muscles, although the Roman scholar Aulus Cornelius Celsus (42 BC–37 AD) advised against surgery, caustic medicines and cautery.

The pessimistic period

Galen (131–203 AD), the legendary Greek physician who worked among the Romans refined Hippocrates' theory that breast cancer was caused 'by the particular humor that prevails in the body'. Galen attributed cancer to an excess of black bile in the body. This systemic concept must have accorded well with the prospects of cure for women with breast cancer. Despite this, Galen excised those tumours that were removable, recommending excision through surrounding healthy tissue. The control of haemorrhage was by the use of pressure on surrounding veins as ligatures were thought to cause local recurrence of breast cancer. Leonidus (180 AD) was more concerned about haemorrhage and he used the knife and cautery alternately as he proceeded around the tumour until the breast had been amputated. This method of amputation as well as the avoidance of ligatures persisted for more than 1000 years and must have been a totally horrific experience without anaesthesia.

Little progress was made during the Dark Ages and surgery was discouraged by the Church, cautery and caustics remaining the mainstay of treatment. In France, Ambrose Paré (1510–90) excised small breast tumours but substituted sulphuric acid for hot cautery. Large tumours were treated with milk, ointment and vinegar. A variety of other topical treatments in this era included goat's dung, frogs, laying on of (preferably royal) hands and compression of the tumour with lead plates. Towards the end of the sixteenth century, new techniques were introduced to

© Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
0521496322 - Medical Therapy of Breast Cancer
Edited by Zenon Rayter and Janine Mansi
Excerpt
More information

surgery, Vesalius (1514–64) used ligatures instead of hot cautery when excising breast cancers. Guillemeau (1550–1601) advocated removal of the pectoralis muscle along with the breast. Severinus (1580–1659) advocated removal of axillary lymph nodes along with the breast and both he and Paré were among the first to appreciate that axillary lymph nodes were part of the malignant process. During the seventeenth century, various instruments began to be developed which allowed very rapid amputation of the breast, perhaps in as little as 2 or 3 seconds. The majority of these techniques involved using metal rings or forks to transfix the breast and distract it from the chest wall, thereby allowing rapid amputation with either a knife or a hinged scythe. The large wounds thus created took months to heal and therefore these were gradually abandoned. During this period cancer remained conceptually a systemic disease. After the discovery of the lymphatic system, Descartes (1596–1650) proposed a lymph theory of the origin of breast cancer that was perpetuated by John Hunter (1728–93), who taught that breast cancer arose when defective lymph coagulated. This was conceptually little better than Galen's black bile theory, but it may have been a stimulus for encouraging surgeons to remove obviously affected axillary lymph nodes.

The optimistic period

In 1757, a French surgeon, Henry LeDran, advanced the theory that cancer began in its earliest stages as a local disease (LeDran, 1757), spread first to the lymph nodes and subsequently entered the circulation. This theory offered the hope that surgery might cure the disease if performed sufficiently early. Other surgeons embraced this pivotal concept during the nineteenth century and it gradually replaced the humoral theory of breast cancer, although, almost a century later, Henry Arnott still felt obliged to reiterate the local origin of breast cancer (Arnott, 1871). With the acceptance of the local origin of cancer, the principles of curative surgery were to perform wide *en bloc* operations at the earliest moment. As early as 1773, Bernard Peyrilhe advised an operation that removed the cancerous breast with the axillary contents and the pectoralis muscle, the same operation introduced by William Halsted 100 years later. Lorensius Heister (1683–1758) removed ribs as well if necessary, an operation still occasionally performed today for stable local disease.

During the nineteenth century great advances were made in science and medicine that included the introduction of general anaesthesia in 1846, antisepsis in 1867 and microscopic pathology. By the end of the nineteenth century, Beatson had demonstrated that breast cancer was hormonally dependent in at least a proportion of patients (Beatson, 1896) and X-rays and radium had been discovered. The results of surgery for cancer of the breast at this time were still poor, partly because of a high operative mortality (up to 20%) due to overwhelming

© Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
0521496322 - Medical Therapy of Breast Cancer
Edited by Zenon Rayter and Janine Mansi
Excerpt
More information

infection. Even those patients who survived rarely lived longer than 2 years. Sir James Paget (the eminent surgeon from Guy's Hospital, London) confessed to never having seen a cure. However, the two forces that pushed radical surgery forward were the theory of local origin and the need to eliminate local recurrence, and these reinforced each other.

In 1867, Charles Moore at the Middlesex Hospital in London renewed the case for the local origin of breast cancer when he published a paper in which he observed that recurrences after limited operations for breast cancer were generally near the scar and that their pattern suggested centrifugal spread from the original site (Moore, 1867). His principles of surgical cure were to remove the whole breast (including as much skin as was felt to be 'unsound'), avoiding cutting into the tumour, and removal of diseased axillary glands as advocated by Peyrihle nearly 100 years earlier. The importance of Moore's paper lies in the fact that it produced evidence for the local origin of breast cancer and the routine removal of the breast is clearly traceable to Moore. Routine removal of the axillary glands is also believed to be due to Moore's influence as although he originally advocated the routine removal of 'diseased' glands, he subsequently became aware of the difficulty in knowing whether the glands were involved or not and stated that they can never be assumed to be normal (Power, 1934–35). Banks in Liverpool subsequently continued to argue for routine axillary surgery and in a paper presented in 1882, he reported 46 cases in whom he had routinely removed axillary nodes (Banks, 1902). Küster in Berlin had also advocated routine axillary dissection with mastectomy as early as 1871 (Küster, 1883) with the effect of drastically reducing axillary recurrence to 1% (Schmid, 1887). The next structure to receive attention was the pectoralis fascia. With the advent of the microscope and developments in pathological anatomy, it was discovered that the pectoralis fascia was occasionally microscopically involved with tumour not obvious to the naked eye. Von Volkman in Germany was one of the first to supplement removal of the breast and axillary contents with routine removal of the pectoralis fascia (Halsted, 1894–95). A view that went further was proposed by Heidenhain, after microscopically examining Küster's cases, who suggested removal of the entire pectoralis muscle if the cancer was infiltrating part of the fascia or muscle (Heidenhain, 1889).

William Halsted, professor of surgery at Johns Hopkins Hospital in Baltimore, USA was aware of developments in Germany and also advocated removal of the entire pectoralis major muscle save occasionally for its clavicular portion. Halsted's operation employed a tear-drop incision, removing so much skin that grafting was subsequently required, removing the whole breast, pectoralis major and the axillary contents after dividing pectoralis minor. In 1894 he published the results of 50 patients so treated with a dramatic fall in local recurrence to 6%

© Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
0521496322 - Medical Therapy of Breast Cancer
Edited by Zenon Rayter and Janine Mansi
Excerpt
More information

compared with the 56–81% reported in Europe (Halsted, 1894–95). By the current definition of local recurrence this would actually represent 18% over a relatively short follow-up. Nevertheless, after 37 years, this had only risen to 31.5% in this group of patients (Lewis & Rienhoff, 1932). The radical mastectomy was an operation whose time had arrived. Professor Willie Meyer of the New York Postgraduate Medical School reported a similar operation in 1894 (Meyer, 1894). The differences in details of the operative technique were that Meyer used a diagonal incision, dissected the axillary contents first and excised pectoralis minor, a modification which Halsted subsequently adopted. The radical mastectomy operation was supported conceptually by the centrifugal permeation theory proposed by William Sampson Handley of London, who stated that cancers originated at one focus and spread from it exclusively through lymphatics. This lymphatic spread was by growth in continuity (permeation) rather than embolic spread and occurred equally in all directions. Regional lymph nodes halted the progress of permeation only temporarily, but thereafter growth through the lymph nodes allowed haematogenous embolization (Handley & Thackray, 1969). Such was Halsted's reputation as a teacher and surgeon, the radical mastectomy soon became the standard operation for breast cancer worldwide. However, the main achievement of this operation was the reduction of local recurrence rates compared with lesser operations and it became clear subsequently that little had been achieved in terms of overall survival. This may in part have been due to the fact that many patients who underwent radical mastectomy had relatively advanced disease. The contraindications to radical mastectomy were subsequently defined by Haagensen with improved results in terms of local recurrence and overall survival in line with better case selection and earlier diagnosis (Haagensen, 1971).

It soon became apparent that radical mastectomy did not cure patients with breast cancer and Halsted extended his operation by removing supraclavicular lymph nodes after dividing the clavicle. He also occasionally removed internal mammary lymph nodes and this procedure was lent support by the work of William Sampson Handley who advocated treatment of involved internal mammary nodes with interstitial radium (Handley, 1922). This line of study was extended by his son, Richard S. Handley, who routinely biopsied internal mammary lymph nodes during the performance of a radical mastectomy in a series of 119 patients and found metastases in 34% of patients. The radical mastectomy was subsequently extended by a number of surgeons to include removal of internal mammary lymph nodes (Sugarbaker, 1953; Urban, 1964). This 'extended' radical mastectomy was extended even further to include removal of the supraclavicular lymph nodes at the time of mastectomy (Dahl-Iverson & Tobiassen, 1969). Some surgeons even went as far as amputating the upper arm *en bloc* with the

© Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
0521496322 - Medical Therapy of Breast Cancer
Edited by Zenon Rayter and Janine Mansi
Excerpt
More information

mastectomy specimen in an attempt to cure relatively advanced local disease (Prudente, 1949). This increasingly radical progression culminated with the 'super-radical' mastectomy in which the radical mastectomy was combined with excision of supraclavicular, internal mammary and mediastinal lymph nodes, first in two stages and later in one stage (Wangensteen et al., 1956). This procedure was later abandoned because of its high operative mortality of 12.5% and the lack of any improvement in long-term survival.

The realistic period

By the mid twentieth century, surgery for breast cancer had reached its limits. Surgeons began to critically reevaluate the efficacy of radical operations for several reasons. First, it became apparent that radical surgery was unable to cure breast cancer in over a third of patients. A greater awareness of postoperative morbidity such as deformity of the chest, lymphoedema of the arm and occasional irradiation-induced sarcomas led to some surgeons becoming increasingly critical of radical surgery and led to a reevaluation of less radical surgery for breast cancer. Secondly, there had been an enormous explosion of knowledge about the biology of breast cancer, killing off old theories of cancer spread and redefining the indications for surgery. Thirdly, the development of medical oncology added to the therapeutic armamentarium which was available to the extent that adjuvant hormonal therapy and chemotherapy was beginning to lead to statistically significant improvements in survival in patients at high risk of relapse (Chapter 3). Fourthly, earlier diagnosis, advocated for centuries by physicians, had become a reality with the development of high-quality mammography and the introduction of mass screening programmes to detect asymptomatic breast cancer in a number of countries including Sweden, Great Britain and the United States of America. Finally, the possibility of preventing breast cancer in high-risk probands is currently the subject of a number of studies using a variety of agents of which tamoxifen is the best-known example.

The rise and fall of endocrine surgery for metastatic disease

A final legacy of the nineteenth century was the discovery that breast cancer was a hormone dependent tumour, at least in some patients. It had been observed in the nineteenth century that the growth of breast cancer in patients sometimes fluctuated with the menstrual cycle and that the disease grew more slowly in postmenopausal women. However, the landmark observation was that by Thomas Beatson who observed temporary regression of metastatic breast cancer in two patients treated by surgical oophorectomy (Beatson, 1896). For the first time, a systemic treatment for breast cancer became available and its hormone depend-

© Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
0521496322 - Medical Therapy of Breast Cancer
Edited by Zenon Rayter and Janine Mansi
Excerpt
More information

ence demonstrated. The importance of the hormonal milieu was subsequently confirmed by the use of adrenalectomy (Huggins & Bergenstal, 1951) and hypophysectomy (Luft & Olivecrona, 1953). In the one-third of patients who benefited, the mechanism by which this occurred was thought to be oestrogen deprivation and the scientific foundation for this was confirmed by the discovery of the oestrogen receptor (ER) in breast tumours (Jensen et al., 1967). Ablative endocrine surgery has now largely been superseded by the development of medical endocrine therapies. Thus, the oestrogen antagonist tamoxifen has mostly replaced surgical oophorectomy, the aromatase inhibitors (which block peripheral synthesis of oestrogens) have replaced adrenalectomy and the luteinizing hormone releasing hormone (LHRH) agonists have replaced hypophysectomy in the management of patients with metastatic breast cancer.

Introduction of radiation therapy for breast cancer

History

By the beginning of the twentieth century radiotherapy had been shown to be effective in treating breast cancer. Keynes, a surgeon at St Bartholomew's Hospital in London, described the results of conservative treatment of breast cancer using implanted radium needles (Keynes, 1937). Originally used in 50 patients with inoperable breast cancer in whom good local control was achieved, it was extended to 85 patients with stage I disease and 91 patients with stage II disease. Tumour was excised and radium needles were inserted throughout the breast, axilla, supraclavicular fossa and the upper three intercostal spaces. Five-year survival was 71% in patients with stage I disease and 29% in patients with stage II disease. These results appeared to be as good as those achieved by radical mastectomy, but despite this the technique was not widely used due to the limited availability of radium, handling problems and postradiation fibrosis.

In 1932, Pfahler from the United States reported the use of radiotherapy in 1022 patients with breast cancer, of whom 53 had early disease and who had refused or were too frail for surgery (Pfahler, 1932). The 5-year survival of patients with early disease was 80% and even patients with stage II disease fared better than historical controls. In Great Britain, Robert McWhirter of Edinburgh was the foremost proponent of radiotherapy in the mid-twentieth century and he reported the results of simple mastectomy followed by radiotherapy to the supraclavicular, internal mammary and axillary lymph nodes in 759 patients (McWhirter, 1948). The 5-year survival rate of 62% was comparable to that achieved by standard radical mastectomy, implying that radiotherapy was effective in treating nodal disease.

A logical extension of these observations was to investigate whether

© Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
0521496322 - Medical Therapy of Breast Cancer
Edited by Zenon Rayter and Janine Mansi
Excerpt
More information

radiotherapy could be used to treat the primary breast tumour. Much of the pioneering work in this area was done at the Institut Curie in Paris. Thus Baclesse (1965) demonstrated that even relatively large cancers could be successfully treated by giving 66–70 Gy fractionated over a three-month period. Another technique which involved a combination of external beam radiotherapy and an iridium implant extended the role of radiotherapy further (Pierquin et al., 1980). The introduction of iridium implants in the USA (Hellman et al., 1980) popularized conservative surgery for breast cancer and in part was the stimulus to the randomized controlled trials of conservative surgery and radiotherapy subsequently described. Further efforts in this direction confirmed comparable survival to surgically treated patients with operable breast cancer but at the expense of high local morbidity (Hochman & Robinson, 1960). Higher energy sources developed in the 1950s reduced cutaneous morbidity and early survival results indicated that irradiation could be a possible alternative to mastectomy although the issues of long-term morbidity and local tumour control still needed to be addressed (Harris et al., 1983). The realization that long-term side-effects of adjuvant radiotherapy could be serious came with the publication of studies which demonstrated an increased mortality from myocardial infarction after radiotherapy for left-sided breast cancer (Cuzick et al., 1987, 1994).

The first randomized controlled trial of conservative surgery and radiotherapy versus radical mastectomy was performed at Guy's Hospital in London (Atkins et al., 1972). The conservative surgery group underwent only a wide local excision of their tumour and no axillary surgery and received 35–38 Gy to the breast and only 25–27 Gy to the supraclavicular fossa, internal mammary chain and the axilla, whereas the radical mastectomy group underwent an axillary clearance and the same dose of radiation to the gland fields as the conservative surgery group of patients. It was therefore not surprizing that there were significantly more locoregional recurrences (notably in the axilla) in the wide local excision group (25%) than in the radical mastectomy group (7%). Overall 10-year survival was similar in patients with stage I disease (80%), but patients with stage II disease had a significantly worse survival in the wide local excision group (30%) compared with the radical mastectomy group (60%). This was an extremely important finding for two reasons. First, it probably delayed the more widespread adoption of conservative surgery for breast cancer and, secondly, it contradicted the popular belief at that time that local control did not influence survival.

Influence of radiotherapy on local control and survival

There is general agreement that the majority of patients undergoing conservative surgery for breast cancer should have radiotherapy. The indications for radiotherapy after mastectomy are less certain. In patients with good pathological

© Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
0521496322 - Medical Therapy of Breast Cancer
Edited by Zenon Rayter and Janine Mansi
Excerpt
More information

prognostic factors (node negativity, absent lymphovascular invasion, tumour size <2 cm and clear margins) there is general agreement that postoperative radiotherapy is not required. In patients with one or more adverse prognostic factors (presence of lymphovascular invasion, >4 involved lymph nodes, tumour size >4 cm), most clinical oncologists would advise postoperative radiotherapy. It is in the group of patients who may only have one to three nodes involved or only one other adverse prognostic factor that the question of radiotherapy is more controversial. The importance of local control and its effect on survival has recently been highlighted again by the results of three recently published studies.

In the Danish study of high-risk premenopausal women (Overgaard et al., 1997) a total of 1708 women who had undergone mastectomy were randomized to have eight cycles of CMF (cyclophosphamide, methotrexate and 5-fluorouracil) plus radiotherapy to the chest wall or nine cycles of CMF alone. High risk was defined as axillary node involvement, tumour size >5 cm and invasion of skin or pectoral fascia. The median length of follow-up was 114 months. The frequency of locoregional recurrence alone or with distant metastases was 9% in the CMF + radiotherapy group compared with 32% in the CMF alone group. The probability of disease-free survival (DFS) was 48% in the CMF + radiotherapy group and only 34% in the CMF alone group. This translated to an absolute overall survival (OS) difference of 9% (54% for CMF + radiotherapy *versus* 45% for CMF alone). All these differences were highly statistically significant.

In the Canadian study (Ragaz et al., 1997) 318 high-risk premenopausal women undergoing modified radical mastectomy were randomized to receive CMF + radiotherapy or CMF alone. High risk in this study was defined as any pathological lymph node involvement. After 15 years of follow-up, the women assigned to CMF + radiotherapy had a 33% reduction in the rate of recurrence and a 29% reduction in mortality compared with the women randomized to CMF alone.

In the third study, this question was addressed in high-risk postmenopausal women (Overgaard et al., 1999). In this Danish study, 689 women were randomized to adjuvant tamoxifen and radiotherapy and 686 women to tamoxifen alone at a dose of 30 mg daily for one year. Median follow-up was 123 months. Locoregional recurrence occurred in 8% of the women who received radiotherapy plus tamoxifen and in 35% of those who received tamoxifen alone. DFS and OS was also much higher in the group who received adjuvant radiotherapy (36% vs. 24% for DFS; 45% vs. 36% for OS) at 10 years. One criticism of this study was that the duration of treatment with tamoxifen was much shorter than currently practised.

These studies have highlighted the importance of local control on survival and suggest that micrometastases in locoregional lymphatics are a potent source of

© Cambridge University Press www.cambridge.org

CAMBRIDGE

Cambridge University Press
0521496322 - Medical Therapy of Breast Cancer
Edited by Zenon Rayter and Janine Mansi
Excerpt
More information

systemic metastases. They also suggest that eradication of locoregional metastases improves survival. These studies potentially may increase the use of adjuvant radiotherapy in those patients who have undergone mastectomy and who have any adverse prognostic risk factors. These and other studies and their significance are further discussed in Chapter 4.

Timing of radiotherapy

The majority of patients undergoing breast conserving surgery will be treated with radiotherapy and, as we have seen, there has been a resurgence of interest in the use of radiotherapy after mastectomy. Until recently, the majority of patients who were node negative may not have been offered systemic therapy, but with the increasing use of adjuvant chemotherapy in this group of patients as well as those who are node positive, the question of sequencing these two treatments has become a topic of great interest. Recently, it has been observed that the order in which radiotherapy and chemotherapy are given may have a bearing on outcome. In a retrospective study of patients who had undergone breast-conserving surgery, it was observed that the actuarial rate of local failure in the breast at 5 years was 4% in patients who received radiotherapy followed by chemotherapy, but rose to 41% in patients who had the reversed order (or sequence) of treatments (Recht et al., 1991). This prompted the introduction of a randomized sequencing trial which has recently been published. The increased risk of local recurrence was again noted in the patients randomized to receive all their adjuvant chemotherapy prior to radiotherapy but this group were observed to benefit in terms of DFS as well as OS. The reverse was seen in patients who received radiotherapy immediately after surgery followed by systemic therapy (Recht et al., 1996).

Combined treatment would seem to be the answer to this controversy but carries with it problems regarding the effects of combined treatment on cosmesis and tolerability. There is a suggestion that concurrent treatment with radiotherapy and chemotherapy produces a worse cosmetic outcome in the preserved breast than sequential treatment (Gore et al., 1987) due to an increase in breast fibrosis. This observation has since been noted by some workers (Taylor et al., 1995), but not by others if methotrexate or doxorubicin is omitted at the time that the radiotherapy is given (Wazer et al., 1992). Combined treatment with radiotherapy and chemotherapy has also been found to increase damage to normal tissues such as bone marrow, skin, lungs, ribs and brachial plexus (McCormick, 1997). These issues and attempts to resolve them are further discussed in Chapter 4.

Theoretical considerations in the spread of breast cancer

The permeation theory of breast cancer spread was the stimulus to the development of increasingly radical surgery. This theory was the first casualty of a greater

© Cambridge University Press www.cambridge.org