

Medical Therapy of Breast Cancer

Edited by

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History of breast cancer therapy

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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

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

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

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%

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

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 post-menopausal 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-

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

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 surprising that there were significantly more loco-regional 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

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

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

understanding of the biology of breast cancer. In 1931 Gray demonstrated that the lymphatics around a primary breast tumour were neither obliterated nor filled with cancer cells, even when axillary nodes were involved by tumour (Gray, 1938–39). This weakened the *en bloc* principle of radical surgery and contributed to the rationale for the less disfiguring modified radical mastectomy in which the breast is removed together with the axillary contents, whilst preserving the pectoralis major muscle. The great proponents of this operation in the 1930s were Patey in England and subsequently Auchincloss and Madden in the United States (Patey & Dyson, 1948; Madden, 1965; Patey, 1967; Auchincloss, 1970). In 1955, Engell demonstrated venous dissemination of breast cancer cells from early operable tumours. This also dealt a blow to the permeation theory which stated that haematogenous spread of tumours occurred only very late in the pathophysiology of breast cancer (Engell, 1955). Subsequently, Fisher and Fisher's work demonstrated that lymph nodes were poor barriers to the spread of cancer cells. In a classic series of experiments in rabbits, they demonstrated that tumour cells could pass easily through lymph nodes into efferent lymphatics and also into veins through lymphaticovenous communications (Fisher & Fisher, 1966, 1967).

The above observations helped to foster a new attitude towards the theory of breast cancer spread which in turn led to a new era in the surgery of breast cancer. It became apparent that radical surgery had reached its anatomical limits without contributing to a reduction in mortality from breast cancer. This was because the concept of local origin provides a basis for cure only if the diagnosis can be made before dissemination has taken place. The stage at which an occult or even symptomatic neoplasm disseminates is extremely variable and is dependent on many factors. One factor long thought to enhance tumour cell dissemination is the effect of handling the tumour during surgery. Trauma to tumours increases both cell shedding and metastasis in animal models (Tyzzer, 1913; Liotta et al., 1976). Early studies of tumour cell shedding in humans were beset by problems with sampling and cell identification and this led to a decline in interest in the subject. Recently, there has been renewed interest in this proposed mechanism of tumour cell dissemination. This is because of an enhanced ability to detect more reliably small numbers of carcinoma cells among large numbers of haematopoietic cells using monoclonal antibodies against epithelial-restricted epitopes (Leather et al., 1993; Pantel et al., 1993) or using quantitative polymerase chain reaction (Smith et al., 2000). A recent study using very sensitive immunohistochemical techniques on selective venous samples before, during and after breast cancer surgery has demonstrated increased shedding of breast cancer cells into the circulation during surgery (Choy & McCulloch, 1996). Furthermore, the likelihood of cell shedding was directly related to tumour angiogenesis as measured by vascular density of the tumour (McCulloch et al., 1995).

However, tumour angiogenesis is probably not the only mechanism involved in

the ability of a tumour to metastasize. Transformed cells also require a reduction in adhesiveness to detach themselves and enter the circulation (Nigam & Pignatelli, 1993). Thus, for migration to occur, the affinity between cancer cells and endothelium or lymphatic channels needs to change. For a cancer cell to attach to a particular target organ, further changes in expression of adhesion receptors in the invading cell and the target tissue are necessary. A prerequisite for these cells to form a metastasis is an increase in re-expression of intercellular adhesion receptors coupled with a capacity to grow independently (Aznavorian et al., 1990; Liotta & Stetler-Stevenson, 1991). Two types of receptors mediate cellular adhesion: those that play a part in intercellular interaction and those that regulate interactions between cells and their surrounding extracellular matrix (a scaffold of glycoproteins and collagens supporting the cells). The main receptors responsible are integrins, cadherins, selectins and members of the superglobulin family (Hynes, 1992). Integrins are the prime mediators of cell-matrix interactions and cadherins of intercellular interactions. Recently a variety of integrin receptors have been demonstrated to be expressed in some breast cancer cell lines and have been shown to have some relationship to the invasive potential of these cell lines *in vivo* (Gui et al., 1995). Likewise, the cell adhesion molecule E-cadherin has been shown to be important in the process of invasion (Marcel et al., 1994) and the E-cadherin/catenin complex can be upregulated by the antioestrogen tamoxifen, thus inhibiting invasion *in vitro* (Bracke et al., 1993).

Another mechanism by which the invasive ability of a cancer cell may be enhanced is by the production of enzymes which can degrade the basement membrane. Thus, tumour expression of the proteolytic enzymes cathepsin D (Joensuu et al., 1995) and plasminogen activator (Janicke et al., 1991) has been demonstrated to be related to poorer prognosis, especially in patients with node-negative disease. The role of the nonmetastasizing protein nm23 (Royds et al., 1993) is still poorly understood.

This increasing understanding of tumour biology may lead to new strategies in our ability to moderate the metastatic potential of cancer cells in the near future. It also partially explains why ever-increasing local surgery has failed to impact on the long-term survival of patients with breast cancer. The development of high-quality mammography, which can now detect tumours of only a few millimetres in diameter, has increased the proportion of patients suitable for conservative surgery. Finally, the introduction of the concept of the randomized prospective trial as a scientific tool has demonstrated the efficacy of conservative surgery when combined with radiotherapy compared with radical surgery. All these factors have contributed to the evolution and acceptance of conservative surgery for operable breast cancer.

Evolution of conservative surgery for breast cancer

Surgery of the breast

The last 20 years has seen a change in the management of the tumour within the breast from mastectomy to breast-conserving surgery (Harris et al., 1987). This trend has been based on the results of a number of retrospective studies (Levene et al., 1977; Peters, 1977; Calle et al., 1978; Hellman et al., 1980; Durand et al., 1984; Rayter et al., 1990) and prospective randomized clinical trials (Veronesi et al., 1981; Sarrazin et al., 1984; Fisher et al., 1985a, 1989). These retrospective studies suggested that breast-conserving surgery produced similar results in terms of local control and survival compared with historical and contemporary controls treated by mastectomy and this was confirmed by the results of the prospective randomized controlled trials.

The acceptability of breast-conserving therapy has increased to the level of accepted practice for early breast cancer and this has been due to the results of prospective randomized clinical trials (Fisher et al., 1989; Sarrazin et al., 1989; Veronesi et al., 1990a; Blichert-Toft et al., 1992). The six studies cited all have follow-up of between 6 and 13 years and conclusively demonstrate similar loco-regional recurrence rates and survival in patients treated by breast-conserving therapy compared with patients treated by mastectomy for stage I and II breast cancer (Table 1.1). The only exception occurred in an early trial conducted in London which suggested that breast-conserving therapy had an adverse effect on survival compared with mastectomy (Hayward & Caleffi, 1987), but this study has since been criticized for using a combination of treatments which today would be considered inadequate.

These studies have established breast-conserving therapy for the treatment of stage I and II (early) breast cancer. However, not all patients with early breast cancer are suitable for breast-conserving techniques, and other factors which need to be taken into account when considering the type of surgery as the initial treatment are the size of the tumour in relation to the size of the breast and the location of the tumour in relation to the nipple-areolar complex. Therefore, it may be entirely appropriate to perform a mastectomy for a stage II tumour (T2, 2–5 cm diameter) if the affected breast is small, or for any tumour located immediately behind the nipple-areolar complex as breast-conserving surgery in these circumstances will produce a poor cosmetic result at best, or achieve inadequate tumour clearance at worst, a situation known to predispose to local recurrence within the breast (Dixon, 1995).

The use of breast-conserving techniques has been a stimulus to research into the extent of tumour within the breast and to how this might influence the extent of a local excision. Foci of tumour in addition to but separate from the main tumour

Table 1.1. Randomized trials comparing conservative surgery with and without radiotherapy and radical surgery

Authors	Treatment	No. of patients	Follow-up (yr)	Local relapse (%)	Survival
Hayward & Caleffi, 1987	RM + RT	186	10	14	60
	LE + RT	190	10	68	28
Veronesi et al., 1990a	RM	349	13	2	69
	QUART	352	13	3	71
Fisher et al., 1989	MRM	590	8	8	71
	LE + AD	636	8	16	71
	LE + AD + RT	629	8	6	76
Sarrazin et al., 1989	MRM	91	10	10	80
	LE + AD + RT	88	10	6	79
Lichter et al., 1992	MRM	116	5	10	85
	LE + AD + RT	121	5	17	89
Blichert-Toft et al., 1992	MRM	306	2	4	76
	LE + AD + RT	313	2	2	80

MRM modified radical mastectomy; QUART Quadrantectomy; LE local excision; AD, axillary dissection; RT radiotherapy.

mass can be detected in the majority of resected breast cancers (Holland et al., 1985). However, it is important to distinguish between foci of cancer in direct relation to the main tumour mass (multifocality) and independent foci of tumour elsewhere in the breast (multicentricity). Multifocal involvement of the breast is common, may be extensive and may consist of microscopic foci of the invasive cancer, emboli of cancer in lymphatics or vascular spaces, or most often, intraductal cancer which can occur at a distance of more than 2 cm away from the site of the primary tumour in up to 10% of cases (Holland et al., 1991). In most cases the associated intraductal involvement has a segmental distribution in the breast; that is, along anatomical boundaries within one of the breast lobes. These studies have implications regarding the extent of local excision when combined with radiotherapy and the feasibility of breast-conserving surgery if irradiation to the preserved breast is to be withheld postoperatively.

The above observations naturally lead on to the unresolved questions regarding the optimal implementation of breast-conserving techniques. One such issue is the extent of breast resection required in patients also receiving postoperative irradiation. Gross excision of the tumour is obviously necessary but the extent of resection of 'normal' surrounding breast tissue is still a matter of debate. Some

data regarding this issue can be gleaned from the results of the randomized trials of breast-conserving therapy even though they did not specifically address this issue. The National Surgical Adjuvant Breast Project trial (NSABP B06, Fisher et al., 1989) employed a limited gross excision of the tumour (referred to as 'lumpectomy') whereas the Milan trial (Veronesi et al., 1990a) employed an operation which removed a larger area of breast tissue (referred to as 'quadrantectomy'). Local recurrence in the conserved breast was less frequent after 'quadrantectomy' than after 'lumpectomy' (3% vs. 8%). This comparison is made difficult by the fact that tumours in the NSABP study were larger (up to 4 cm, a factor likely to increase local recurrence) than in the Milan trial which only included patients with tumours less than 2 cm and length of follow-up was different in the two trials (NSABP, 8 yr; Milan, 13 yr).

It is customary for patients undergoing breast-conserving surgery for breast cancer to receive postoperative irradiation. In the NSABP study, one group of patients were randomized to undergo 'lumpectomy' without the addition of postoperative irradiation, and in these patients local recurrence within the treated breast reached 39% at 8 years compared with 10% in the patients who underwent 'lumpectomy' and postoperative irradiation (Fisher et al., 1989). A more recent study from Milan has specifically addressed the question of the necessity for postoperative irradiation in the preserved breast (Veronesi et al., 1993) in patients with small breast cancers (<2.5 cm diameter) whose primary surgery consisted of quadrantectomy and axillary clearance. This study randomized 567 women between surgery alone and surgery with postoperative irradiation. Patients who had positive axillary nodes also received adjuvant systemic medical therapy. After a median length of follow-up of 39 months, only 0.3% of patients undergoing surgery and postoperative irradiation developed a local recurrence compared with 8.8% of patients undergoing surgery alone. An analysis of the major factors contributing to a high rate of local recurrence in patients undergoing surgery alone were younger age (<45 years, local recurrence rate 17.5%) and the presence of an extensive intraduct component. Patients undergoing surgery alone over the age of 55 had a low incidence of local recurrence (3.8%) and it may be that older women with a small completely excised tumour may be treated by surgery without the addition of postoperative irradiation to the breast. There is not sufficient information available on whether patients with tumours exhibiting histologically favourable features may be spared postoperative irradiation after primary surgery. The current British Association of Surgical Oncology (BASO) II study for patients who have had small well-differentiated or special-type cancers seeks to randomize patients in a 2 × 2 design to either observation, tamoxifen, radiotherapy to the breast or to the combination of tamoxifen and radiotherapy.

Axillary surgery

Since breast cancer commonly metastasizes to the axilla, no discussion about local treatment is complete without a discussion on the role of axillary surgery. The likelihood of axillary node involvement is related to the size of the primary tumour. The presence or absence of axillary node metastases is still the best prognostic factor (Cancer Research Campaign Working Party, 1980; Fisher et al., 1985b). Knowledge of axillary node status also provides a rational basis for selection of patients for adjuvant systemic therapies, especially in those patients who have a higher number (>4) of involved lymph nodes, where more aggressive adjuvant chemotherapy regimens would be advised.

The goal of axillary surgery has therefore evolved from increasing the likelihood of cure to, more simply, preventing locoregional recurrence in the axilla and obtaining the best prognostic information. A variety of early trials focused on the treatment of regional nodes. These trials consisted of the following important studies:

- comparison of radical mastectomy plus postoperative irradiation with simple mastectomy plus postoperative irradiation (Brinkley & Haybittle, 1966; Bergdahl, 1978);
- comparison of radical mastectomy with radical mastectomy plus postoperative radiation (Paterson & Russell, 1959);
- comparison of simple mastectomy plus postoperative irradiation with radical mastectomy (Bruce, 1971);
- comparison of simple mastectomy plus postoperative irradiation with mastectomy extended to the supraclavicular and internal mammary nodes (Kaae & Johansen, 1969);
- comparison of simple mastectomy with simple mastectomy plus postoperative irradiation (Murray et al., 1977);
- comparison of radical mastectomy with radical mastectomy plus internal mammary node dissection (Lacour et al., 1976; Veronesi & Valagussa, 1981);
- comparison of simple mastectomy with radical mastectomy (Fisher et al., 1977).

The results of these studies suggested that the stage of the disease was the most important predictor of survival (especially node status) and variations in treatment did not affect overall survival. However, postoperative irradiation was effective in improving local control of breast cancer even though this was not translated into improved survival. The same was true for surgical removal of internal mammary and axillary lymph nodes. Finally, it was apparent that the incidence and severity of lymphoedema caused by surgery was increased with the addition of postoperative radiotherapy.

Despite these studies, axillary surgery is an area in which controversy continues to exist, especially the debate over the type of axillary surgery which should be

performed. Recently, some authorities have favoured axillary clearance rather than the more conservative surgical procedure of axillary sampling (Fentiman & Mansel, 1991). The rationale of surgery to the axilla is that it provides the best prognostic indicator available (in terms of the number of involved lymph nodes) and thereby provides a rational basis on which to select patients for adjuvant systemic medical therapy. If axillary surgery is performed, what is the best procedure? Proponents for axillary clearance and axillary sampling have recently debated this issue in the literature (Davidson, 1995; Greenall, 1995). The arguments in favour of axillary clearance are that it achieves the best local control of axillary disease, provides the best prognostic information, spares the axilla from postoperative irradiation and therefore avoids the increased morbidity associated with surgery combined with irradiation which can lead to disabling lymphoedema of the arm in up to 40% of patients, compared with 6% in patients undergoing axillary surgery alone (Davidson, 1995). The arguments in favour of a properly performed axillary sampling procedure (removing at least four lymph nodes) are that it also provides excellent prognostic information, is associated with low morbidity, avoids extensive axillary surgery in patients with node-negative disease and has been demonstrated to be just as efficacious in achieving a low rate of axillary recurrence when combined with postoperative irradiation in node-positive disease, as does axillary clearance (Greenall, 1995).

Another controversy regarding axillary surgery is whether it needs to be performed at all. It is nearly 50 years since McWhirter suggested that irradiation was a credible alternative to surgery in the management of axillary metastases (McWhirter, 1948) but it is only recently that the case for the routine use of axillary surgery has again been questioned. It has been argued that the heterogeneity of breast cancer dictates that individual patients should be treated on their merits. It is now generally accepted that patients with ductal carcinoma in situ (DCIS) should not undergo axillary surgery (Chapter 2) because theoretically there should be no spread to the axillary lymph nodes. An exception to this is in patients with extensive DCIS (> 5 cm diameter) which is associated with microinvasion and a significant risk of axillary node involvement. Another group of patients who can reasonably be spared axillary surgery are the elderly (age > 70 years) who may be adequately managed by wide excision of the tumour and adjuvant tamoxifen. It has also been argued that those patients in whom adjuvant endocrine therapy would be advised on the basis of parameters derived from the primary tumour (for example, tumour size > 2 cm and positive oestrogen receptor status) could also be spared axillary surgery (Harris et al., 1992). With the introduction of breast screening programmes in the United Kingdom and elsewhere, an increasingly greater number of small, good prognosis breast cancers are being detected. In the past, patients with these small tumours have undergone axillary surgery to

pathologically stage the disease but it has become increasingly obvious that patients with screen-detected cancers have a relatively low (25%) rate of lymph node metastases. In a recent large series of patients the incidence of positive axillary lymph nodes was documented according to the size of the invasive component of the primary tumour (Silverstein et al., 1994). Thus, T1 tumours (<2 cm) were subdivided further according to size (T1a <5 mm, T1b 6–10 mm, T1c 11–20 mm) and the incidence of axillary lymph node metastases recorded within each size category. The incidence of positive axillary lymph nodes for T1a tumours was only 3% but increased markedly for tumours larger than 5 mm (T1b 17%, T1c 32%). However, even for patients with T1b and T1c tumours, up to half the patients with positive axillary nodes will only have micrometastases or only one or two lymph nodes involved. Only 2%, 6% and 9% of all T1a, T1b and T1c invasive cancers respectively have more than three positive lymph nodes (Cady, 1994). It has been argued therefore that patients with T1a tumours should not undergo axillary surgery at all. Other situations in which axillary surgery could probably be avoided are in patients with mammographically detected cancers less than 1 cm in diameter with favourable histological features and in patients with small tumours of special type such as tubular, papillary and colloid cancers in which the incidence of positive axillary nodes is very small (Cady, 1994). The best way of substantiating these opinions is by means of a randomized controlled trial to determine whether axillary surgery confers any survival advantage, although this would require the recruitment of very large numbers of patients requiring prolonged follow-up.

Sentinel node biopsy in the management of the axilla

There has been much interest recently in the concept of the sentinel node in the management of the axilla in breast cancer. Oliver Cope referred to the 'Delphian node' in 1963 as the lymph node that will 'foretell the nature of a disease process' affecting a nearby organ. Therefore, the first lymph node to receive lymphatic drainage from the site of a tumour should be the first site of lymphatic spread. The corollary of this theory is that a tumour-free sentinel lymph node implies the absence of lymph node metastases in the whole of the lymphatic basin to which that organ drains. This concept was introduced into clinical practice in the management of penile carcinoma (Cabanes, 1977) and was based on the anatomical location of the lymph nodes around the superficial epigastric vein. However, the technique employed then (lymphangiography) was relatively crude and the significance of the concept was not appreciated at that time.

This concept was subsequently investigated in the management of cutaneous malignant melanoma by Morton and colleagues. To localize the sentinel lymph node, they developed intraoperative mapping using intradermal vital blue dye to

stain the lymphatics, followed by careful surgical exploration of the regional lymphatic basin (Morton et al., 1992). In this series of 237 patients, a sentinel node or nodes was identified in 82% of cases. In all, 72% of patients had a single sentinel node, 20% had two sentinel nodes and 8% had three sentinel nodes. Of the 194 patients who had a sentinel node identified, 40 (21%) had lymph node metastases and only two patients had metastatic deposits in nonsentinel nodes in the absence of tumour in the sentinel lymph node; the false negative rate was therefore only 1%. Of importance was the observation that of the 40 lymph nodes with deposits of tumour, only 23 were diagnosed using haematoxylin and eosin (H & E) staining, the remainder being identified by immunohistochemistry.

The use of vital blue dyes has some drawbacks, notably difficulty in visualizing the blue-stained lymphatics and the passage of dye to nonsentinel lymph nodes. Shortly after Morton's report, radiolabelled colloids were introduced which allowed the identification of radioactive sentinel lymph nodes preoperatively by scintigrams and peroperatively by means of a hand-held gamma probe (Alex & Krag, 1993; van der Veen et al., 1994). A further study has combined the use of vital blue dye and a gamma probe in a larger group of patients and has shown that all the nodes stained blue also contained radioactive colloid (Krag et al., 1995).

Identification of the sentinel lymph node has recently been extended to patients with breast cancer. Studies which have employed peritumoral injection of a blue dye alone have had success rates which vary from 50% to 100% in terms of the ability to detect the sentinel nodes (Folscher et al., 1997, Giuliano et al., 1994). This variability is probably due to the type of blue dye used and the learning curve involved in using a new surgical technique. If the false negative rate is taken as the proportion of sentinel nodes which are negative for tumour in patients subsequently found to be axillary node positive on more formal axillary staging, then false negative rates vary from 0% to 17% (Table 1.2). For routine use, sentinel lymph node biopsy would need to be more reliable.

Another method of localizing the sentinel lymph node is by the use of a radionuclide and a number of studies using this technique have now been reported (Table 1.2). Essentially, the technique involves a peritumoral injection of a technetium-99-labelled carrier (human serum albumin, sulphur colloid and antimony sulphate have been used) preoperatively. A scintigram may be taken at various times after injection preoperatively and this may make siting of the axillary incision more precise in relation to the sentinel lymph node. Surgery is then performed 2–24 hours after injection of the radioactive colloid and a gamma probe is then used to identify the lymph node peroperatively. In the largest study which has compared preoperative lymphoscintigraphy with intraoperative localization of the sentinel node using a gamma probe (Veronesi et al., 1997), 163 patients underwent a subdermal injection above the tumour site with

Table 1.2. Studies of sentinel lymph node biopsy in breast cancer

Author/Year	Technique	No. of patients	Detection rate (%)	False –ve rate (%)	Predictive rate (%)	Node +ve rate (%)
Giuliano et al., 1994	Blue dye	174	66	12	96	36
Folscher et al., 1997	Blue dye	79	40	12	85	51
Flett et al., 1998	Blue dye	68	82	17	95	31
Offodile et al., 1998	Gamma probe	41	98	0	100	45
Veronesi et al., 1997	Scintigraphy + gamma probe	163	98	5	98	53
Pijpers et al., 1997	Scintigraphy + gamma probe	37	92	0	100	34
Borgstein et al., 1998	Scintigraphy + gamma probe	130	94	2	98	42
Roumen et al., 1997	Scintigraphy + gamma probe	83	69	4	96	40
Albertini et al., 1996	Scintigraphy + blue dye	62	92	0	100	32
Cox et al., 1998	Gamma probe + blue dye	466	94	1	100	23
O’Hea et al., 1998	Scintigraphy + gamma probe + blue dye	59	93	15	95	36

5–10 MBq technetium-99-labelled human serum albumin the day before surgery. Scintigraphic images were taken of the breast and axilla at 10, 30 and 180 minutes and the skin was marked over the first lymph node that became radioactive. The hand-held gamma probe was used to localize the sentinel lymph node(s) which was then excised successfully in 98% of patients. This node accurately predicted the status of the remainder of the axilla in 98% of cases with a false negative rate of 5%. False negative rates in other (albeit smaller) studies vary from 0% to 4% (Table 1.2). Some studies have also been performed using the gamma probe alone, without the use of preoperative lymphoscintigraphy. These have generally been on small numbers of patients, although the authors have achieved similar results as in those studies which have employed preoperative lymphoscintigraphy.

There have been some studies which have used a combination of a blue dye technique and a radionuclide technique, with and without preoperative lymphoscintigraphic scanning, but all using a gamma probe at operation to identify the sentinel lymph node. Although the studies are not strictly comparable in that different blue dyes, different carriers and different doses of technetium-99 were used, all three studies found that the addition of the radionuclide technique to the blue dye technique increased the success rate for identification of the sentinel lymph node from approximately 70% to 93% (Table 1.2). In addition to these variations in the substances and doses of radionuclide, it is worth noting that the time interval between injection of the radionuclide and surgery also varied in all of the studies discussed. Finally, of great importance regarding the timing of surgery after injection of radionuclide is the site of injection within the breast. Thus, subdermal injection near the site of the tumour leads to more rapid migration of the radionuclide to the axillary nodes than peritumoral injection.

These studies suggest that the concept of the sentinel lymph node in breast cancer spread is valid. This is supported by new histopathological studies which confirm that the sentinel lymph node is the axillary node which is most likely to contain a metastasis (Turner et al., 1997). The incidence of skip metastases varies from 1% to 42% (Boova et al., 1982; Forrest et al., 1982; Rosen et al., 1983; Pigott et al., 1984; Veronesi et al., 1990b) but this has traditionally been based on the anatomical level of the lymph node in relation to pectoralis minor in the axilla. Although the variation in the reported incidence of skip metastases may be due to variations in the technique of axillary clearance, individual anatomical variations and failure to identify lower level micrometastases by conventional methods, it seems highly likely that this variation may also be due in part to variations in local lymphatic flow, either due to variations in lymphatic anatomy, or due to plugging of proximal lymphatics by tumour emboli. This is supported by the fact that the sentinel lymph node may be found in level II nodes in 18–23% of cases (Giuliano et al., 1994; Roumen et al., 1997).