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The Surgeon, Journal of the Royal Colleges of Surgeons of Edinburgh and Ireland
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The impact of the Biomolecular Era on breast cancer surgery

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ARTICLE INFO

Article history:
Received 22 June 2016
Received in revised form
14 September 2016
Accepted 18 September 2016
Available online 2 November 2016

Keywords:
Breast cancer
Molecular biology
Genomics
Surgery

ABSTRACT

Surgery has always played a central role in the management of breast cancer, with local control via complete tumour resection long established as the cornerstone of effective breast cancer therapy. While extensive surgical resection in the form of the Halstead radical mastectomy dominated treatment up until at least the 1970s, the advent of adjuvant loco-regional and systemic therapies has resulted in a decrease in the magnitude of surgical intervention in recent decades. The Biomolecular or "-omics" era initiated with the discovery of the DNA double helix in 1953 and intensified by the completion of the human genome project in 2003 has seen an unprecedented expansion in our understanding of the molecular and genetic heterogeneity of cancer. This review will discuss how the clinical application of this knowledge in the direction of personalised risk assessment and breast cancer treatment has significant implications for modern surgical practice.

Introduction

Breast cancer imposes a substantial global health burden, with approximately 1.7 million women diagnosed and treated worldwide annually.[1,2] Despite an increasing incidence and status as the most commonly diagnosed and second leading cause of cancer death in females, significant progress has been made in the management of breast cancer, with 5-year survival rates improving from only 40% 50 years ago to 87% today.[3] Complete surgical tumour resection is the cornerstone of effective breast cancer therapy. However, since the mid-20th century, the practice of breast cancer surgery has evolved significantly, in large part due to the influence of scientific progress on surgical practice.

The "Biomolecular Era", initiated with the discovery of the DNA double helix by Watson and Crick in the 1950s[4,5] and intensified by the completion of the Human Genome Project,[6] has resulted in an unprecedented expansion in our knowledge and understanding of the heterogeneity of malignant disease. The sequencing of the human genome[6] and the advent of high-throughput molecular profiling[7] has facilitated comprehensive analysis to decipher the molecular mechanisms that underlie breast cancer heterogeneity, tumour initiation and disease progression. Molecular profiling of breast tumours for

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http://dx.doi.org/10.1016/j.surge.2016.09.007

prognostication and prediction of response to therapy has been incorporated into contemporary management strategies in a move towards personalised breast cancer therapy. The development of adjuvant therapies which effectively reduce both distant and loco-regional recurrence,[8–10] and the recognition that tumour biology also impacts local control independently of extent of resection[11] have contributed to a paradigm shift towards increasingly conservative therapeutic surgical approaches.[12]

The availability of genetic mutation analysis for high risk individuals has also transformed the surgeon's approach to the assessment and management of breast cancer risk. Identification of highly penetrant single gene mutations, such as those in *BRCA1* or *BRCA2* have led to an evolution in the role of surgery from purely therapeutic to prophylactic. As a consequence of both the increasing volume of risk-reducing surgery and improved survival of breast cancer patients, surgical techniques have evolved in an effort to maximise aesthetic and quality-of-life outcomes leading to the development of novel breast conservation techniques, skin and nipple-sparing mastectomy and an increasing range of novel reconstructive approaches which have been introduced to the modern breast "oncoplastic" surgeon's armamentarium. Current research is focused on the identification and characterisation of additional low and moderate-risk breast cancer susceptibility loci using genome-wide approaches. The incorporation of these loci in polygenic models to more accurately predict breast cancer risk has the potential to further rationalise screening, surveillance and risk-reduction strategies.

This is an exciting era in the management of breast cancer; contemporary treatment is an intricate multidisciplinary process with surgical management remaining at its core. Clinicians collaborating across disciplines require an in-depth understanding of the molecular and genetic heterogeneity of the disease in order to achieve the goal of individualised treatment.

This review discusses the impact that recent progress in molecular biology has had on the surgical management of breast cancer focusing on the application of molecular profiling tools to rationalise loco-regional breast cancer therapy and the use of gene mutation analysis to guide risk reduction strategies in this era of molecularly tailored and genome-informed personalised care.

Historical perspective – evolution from cancer surgery to surgical oncology

Complete surgical tumour resection has traditionally been the cornerstone of effective breast cancer management. The first evidence for the role of surgery in the treatment of this malignancy dates back to the Edwin Smith Surgical Papyrus (3000–2500 BC) which described early attempts at tumour cauterisation.[13] However, it was not until the mid-19th century that revolutionary scientific advances, including the development of Anaesthesia (Morton, 1846)[14] and Asepsis (Lister, 1867),[15] facilitated major advances in cancer surgery. Surgeons enjoyed a newly-acquired freedom to perform more radical procedures, and en-bloc resection with wide disease-free margins became the primary curative treatment for many solid organ malignancies. In 1849 William Halstead first reported his radical mastectomy comprising extensive resection of all breast tissue, regional lymph nodes and *pectoralis major*,[16] which became the mainstay of breast cancer treatment for subsequent generations of surgeons, despite significant associated physical and psychosocial morbidity.[17] A move towards less radical surgery in the latter half of the 20th century was pioneered by Bernard Fisher and the National Surgical Adjuvant Breast and Bowel Project who hypothesized that there was no biological or scientific rationale for radical surgery as this alone was not always sufficient to control disease progression or metastatic spread.[18] A series of well-designed randomised controlled trials provided evidence that breast conserving surgery (BCS) combined with adjuvant radiotherapy has equivalent survival outcomes to mastectomy (Table 1).[19–26] The move towards breast conservation in the wake of these trials signalled a paradigm shift in our approach to breast cancer surgery, which for the first time was supported by scientific evidence.

The development of systemic adjuvant therapy also redefined the role of surgery in breast cancer treatment.[27,28] Trials of adjuvant systemic chemotherapy alone and in combination with hormonal and/or targeted anti-Her2 therapy provided evidence that systemic adjuvant therapies decreased LRR and distant metastatic disease following surgery.[9,10,28,29] The identification and characterisation of the hormone receptors (Estrogen (ER) and Progresterone (PR)) and the Her2/neu receptor as strong predictors of response to chemotherapeutics, hormonal therapy and targeted anti-Her2/neu monoclonal antibodies[30,31] represented the first clinically relevant move towards an individualised approach to breast cancer treatment based on molecular analysis. This recognition of the effects of tumour biology and the use of systemic therapy on disease control transformed the role of surgical tumour resection; what was once the only curative option became just one weapon in a growing armamentarium of oncologic therapies. Breast cancer surgeons were now entering a new era of multidisciplinary cancer care as "Surgical Oncologists" working in equilibrium alongside other specialist oncologists, considering surgical resection in the context of tumour biology and the contributions of multi-modal therapies to disease control. Since then, the practice of breast cancer surgery has been influenced by scientific progress with an escalating momentum in molecular biology and genetics research, which increasingly informs surgical decision-making regarding when, how and on whom we operate.

Molecular profiling – rationalisation of loco-regional therapy

As adjuvant systemic and targeted therapies have become an important component of breast cancer treatment and contributed to improved prognosis, it has become increasingly evident that there is considerable variation in response to therapy, driving basic and translational research in this field. Recent years have seen rapid technical advances resulting in a multitude of high throughput genomic technologies which have been developed to simultaneously measure variation in