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SURGICAL TREATMENT FOR BREAST CANCER AND AXILLARY METASTASES: HISTORICAL PERSPECTIVE

KIRURŠKO LIJEČENJE KARCINOMA DOJKE I AKSILARNIH METASTAZA: POVIJESNA PERSPEKTIVA

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SUMMARY

Breast cancer (BC) is the most common malignancy to affect females. The first suggestions of BC and its treatment date back to Ancient Egypt, 1500-1600 B.C. Throughout history, the management of BC has evolved from extensive radical mastectomy towards less invasive treatments. Radical mastectomy was introduced by W.S. Halsted in 1894, involving the resection of the breast, regional lymph nodes, pectoralis major and minor. Despite its mutilating effect, it had been the main surgical approach to BC patients until 1948, when Patey and Dyson proposed its modified form that conserved pectoralis major and minor and the level III of axillary lymph nodes. The latter was associated with less postoperative morbidity and improved quality of life. The idea of limited breast tissue resection was introduced in the 1970s by Umberto Veronesi and led to further minimizations of surgery in BC patients until breast conservation became the standard of care for early-stage disease. In the 1990s, intra-

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operative lymphatic mapping and the concept of sentinel lymph node (SLN) biopsy (SLNB) have been developed. SLNB has replaced axillary lymph node dissection (ALND) to be the standard procedure for axillary staging in patients with clinically node-negative BC. Many women have since been spared ALND, including those with negative SLNB or with SLNs involved with micrometastases (0.2-2 mm in size). In the last decade, evidence gathered from new clinical trials suggests that ALND may be safely omitted even in BC patients with 1 or 2 positive SLNs if adjuvant radiotherapy is delivered.

Keywords: *axillary lymph node metastasis, breast cancer, breast surgery, sentinel lymph node*

Introduction

Breast cancer (BC) is the most common cancer in females. From ancient times and the first civilizations, BC has been mentioned throughout the entire human history.[1] The oldest documented case of malignancy of any kind was a case of BC in Ancient Egypt around 1600 B.C. Galen, who in A.D. 200 wrote about BC coming from an excess of black bile, postulated that not all tumours were equally dangerous and suggested a complete removal of BC. The latter had an impact on BC treatment after that. From the first medical records to the present day, human history is full of evidence of BC being a subject of permanent interest and research.[2]

Antiquity

BC can be traced more than 4000 years ago back to ancient Egypt, with the earliest recorded case documented on the 1600 B.C. Edwin Smith Papyrus. The ancient text was found in an Egyptian tomb in Teba in 1862, describing 48 surgical cases, like injuries, fractures, and eight cases of tumours or ulcers of the breast, most likely representing BC. The Papyrus, possibly attributable to Imhotep, provides the oldest clear description of the disease, comparing two of the cases, with "a cool bulging tumour over the breast" and "hot bulging tumour". Besides, the same text provided evidence of the first attempts to treat BC, since the first case was considered incurable, and the second was cured by surgical drainage.[3]

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1 Ekmektzoglou, K.A.; Xanthos, T; German, V.; Zografos, G.C. (2009), Breast cancer: From the earliest times through to the end of 20TH century, *Eur J Obstret Gynecol and Reprod Biol*, 145 (1), 3-8.

2 Papavramidou, N.; Papavramiis, T.; Demetriou, T. (2010), Ancient Greek and Greco-Roman methods in modern surgical treatment of cancer, *Ann Surg Oncol*, 17 (3), 665-7.

3 Lakhtakia, R. (2014), A Brief History of Breast Cancer: Part I: Surgical domination reinvented, *Sultan Qaboos Univ Med J*, 14 (2), e166–e169.

The Ancient Greeks also knew BC. The origin of the word cancer is credited to Hippocrates, the Greek physician, who in 460 B.C. described ulcer-forming and non-ulcer forming tumours, using the terms *karkinos* and *karkinoma,* which in Greek refer to a crab. The term was later translated into Latin by the Roman physician Celsus (28-50 B.C.). The Latin word for crab was *cancer*. Postulating that the human body consisted of four humors, Hippocrates described BC as a humoral disease that develops from an imbalance among the body fluids, blood, phlegm, black and yellow bile corresponding to water, air, earth, and fire. He considered health a right balance among the body fluids, while he believed that the excess of black bile caused BC. He described severe cases of BC in two women. Hippocrates supported a healthy lifestyle regarding the BC treatment and thought that patients with BC should not be surgically treated.[4]

Archigenes of Apamea (1st-2nd century A.D.) was a Roman physician whose surgical method was described in detail by Oribasius (4th century A.D.). He noted that any part of the body, found to be affected by certain carcinomas or by sepsis, should be removed. At the same time, surgery may be avoided in the early-stage disease when medicaments can be used. In an advanced stage of cancer, as he noted, surgery was inevitable. Before excising the tumour, he suggests that the surrounding vessels needed are tied, or the circulation intercepted by a ligature. In the case of a haemorrhage, he suggested cauterization. Finally, the wound should be sutured. Instructions were given for cleaning the wound after 2-3 days with agents against inflammation.[5]

In A.D. 200, Galen also supported the humoral theory of the disease. Like Hippocrates, Galen believed BC was caused by excessive black bile that not being eliminated by the spleen accumulates in the body. He noted that dark-coloured veins around the tumours were responsible for their crab-like appearance. However, unlike Hippocrates, Galen believed that malignant tumours occur more often in women and that not all of them were equally dangerous. He noted that BC was more prevalent in females who were not menstruating. An incision around the tumour and excision was a sort of lumpectomy that Galen had suggested. He advised that the surrounding vessels should be compressed, along with purgative liquids being used before

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4 Mannu, G.S.; Bhalerao, A. (2014), A century of breast surgery: from radical to minimal, *Can J Surg*, 57 (4), e147-8.

5 Sakorafas, G.H.; Safioleas, M. (2009), Breast cancer surgery: An historical narrative, Part I. From prehistorical times to Renaissance, *Eur J Cancer Care (Engl)*, 18 (6), 530-44.

removal to prevent haemorrhage. In these patients, he also suggested the use of other medications, including opium, castor oil, sulfur and licorice.[6]

Leonides of Alexandria (2nd century A.D.) provided the first description of nipple retraction as a sign of BC; he described the procedure of the tumour excision alternated with cautery that served to remove BC without haemorrhage and suggested avoiding excisions in the cases with BC involving the entire breast or invading thorax. Paulus Aagineta (7th century A.D.) also believed that malignant tumours occur as a result of the excess of black bile, with or without ulceration, most frequently in female breasts or uterus. He thought that surgical treatment was not possible for uterus cancer, while for BC was mandatory. He disagrees with mastectomy and cauterization of the area and supported only Galen's approach with the excision of the tumour and its roots.[7]

Middle Ages

The stagnation of medicine persisted throughout the Middle Ages. The studies of the human body were not welcome for religious reasons. To Muslims, even the representation of the human body was strictly forbidden. In the West, the Christian church was strongly opposed to a dissection of human cadavers. Crude and horrifying methods of rapid breast excisions were practised without using anaesthesia, and unique instruments for fast removal were introduced in France by Albucasis and Mondeville in the 13th century and by de Chauliac in the 14th century.[8]

Renaissance

The 16th to 18th centuries represented the golden age. The anatomy of the human body was explored. Medical institutions were founded in Bologna, Pisa, Padua, and Basel. Medical students were taught medicine, while surgical discipline was overgrowing rapidly on the foundations of human research.[9]

In the 16th century, Andreas Vesalius was a Flemish physician who used his descriptions of the human anatomy to perform wide excision as a surgical technique to treat BC. Ambroise Pare supported the widespread removal of

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6 Lukong, K.E. (2017), Understanding breast cancer - The long and winding road, *BBA Clin*, 7, 64–77.
7 Ibid., p. 64-77.
8 Ibid., p. 64-77.
9 Lakhtakia, R. (2014), e166–e169.

BC as an alternative to breast amputation and recommended using vinegar, sweet milk or fatty cream in the treatment of ulcerated tumours. In the 17th and 18th centuries, the Galenic humoral theory was challenged by several physicians. René Descartes proposed the lymphatic theory as an explanation of the BC origin. Franciscus Sylvius expressed his disagreements with the theory of BC resulting from accumulated black bile, suggesting the approach of lymphatic fluids transformation to the acidic base instead. Claude-Deshais Gendron argued that cancers were "nerve-like", coming from nerves and glandular tissue mixed with lymph vessels, with coagulations of the defective lymph making palpable breast tumours. John Hunter advocated the lymphatic theory, suggesting the removal of BC along with the lymphatic spread.[10]

18th and 19th Centuries

In 1713, Bernardino Ramazzini established occupational medicine, with observations that BC in Italian nuns was more frequent compared to married women. What he speculated was that celibacy and nulliparity make reproductive organs unstable, leading to BC.[11]

In the 18th century, the French surgeon, Henri François Le Dran, was one of the first who considered cancer to be a local rather than a systemic disease. He assumed that cancer progressed in stages and first described its potential to progress by lymph and blood vessels, from being localized to being spread.[12] Jean Louis Petit was another French surgeon. He wrote a book *Traité des maladies chirurgicales et des opérations qui leur conviennent*, in which the concept of ablative surgery was described. That included the excision of the breast, palpable axillary lymph nodes, underlying pectoral fascia, and in the case of the tumour affecting the pectoral muscle, the removal of the muscle was also recommended.[13] In the 19th century, Charles H. Moore substantiated his belief that radical mastectomy should be performed along with axillary lymph node clearance by giving an example of a BC patient undergoing an inadequate radical surgery who later experienced tumour recurrence. Moore

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10 Sakorafas, G.H.; Safioleas, M. (2009), 530-44.
11 Lukong, K.E. (2017), 64-77.
12 Sakorafas, G.H.; Safioleas, M. (2010), Breast cancer surgery: An historical narrative. Part II. 18TH and 19TH centuries, *Eur J Cancer Care (Engl)*, 19 (1), 6-29.
13 Tanis, P.J.; Nieweg, O.E.; Valdés Olmos, R.A.; Th Rutgers, E.J.; Kroon, B.B. (2001), History of sentinel node and validation of the technique, *Breast Cancer Res*, 3 (2), 109-12.

conducted the en bloc resection in London, while two other en bloc resections, those of Kuster and Volkmann, ran a parallel course in Germany.[14]

The 19th century brought disinfection, sterilisation and the use of sterile gloves. When anaesthesia became available in 1846, the development of surgery in the next hundred years made rapid progress. Three surgeons stood out for their practice of using the surgical method, which included both the removal of the entire tumour mass and regional lymph nodes. William Stewart Halsted, the American surgeon, was the first one. He published his findings after performing more than 50 surgeries between 1889 and 1894 using the new technique he called "the complete operation", which eventually became known as radical mastectomy. He insisted that cancer was a local illness and that local recurrence must be prevented, encouraging radical breast surgery with axillary lymph node dissection (ALND).[15] Halsted's name soon became synonymous with the removal of the breast, pectoralis major and minor, and axillary lymph nodes en bloc, which became the standard operation for BC in the late 19th century and remained the gold standard until the mid-20th century. Halsted's concern was that the danger of manipulating a BC during surgery might lead to tumour dissemination.[16]

W. Sampson Handley was a London surgeon who believed that cancer spreads from the site of original growth by invasion, and the third surgeon was Bilroth from Germany, who followed the original idea of Lorenz Heister, a German who represented mastectomy and lumpectomy in his book. In contrast to the three surgeons introducing radical surgery with mastectomy and ALND, James Paget questioned the need for such extensive treatment, given the associated risks and regarding the issue of quality of life.[17]

20th and 21st Centuries

In the first half of the 20th century, the knowledge about the biology and epidemiology of BC was growing. After Wilhelm Conrad Röentgen had presented the concept of X-rays in 1896, a couple of years later X-rays were first used for mammography and BC treatment. Thanks to Pierre and Marie Curie, and Antoine H. Becquerel, new radiation sources were discovered. Halsted's

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14 Sakorafas, G.H.; Safioleas, M. (2010), Breast cancer surgery: a historical narrative. Part III. From the sunset of the 19th to the dawn of the 21st century, *Eur J Cancer Care (Engl)*, 19 (2), 145-66.
15 Mannu, G.S.; Bhalerao, A. (2014), e147-8.
16 Lakhtakia, R. (2014), e166–e169.
17 Lukong, K.E. (2017), 64–77.

surgery was the backbone of BC treatment until the mid-20th century, being preserved by Margottini and Veronesi from Milan. They even extended its scope to internal mammary lymph nodes while the American surgeon, Owen H. Wangensteen, reached supraclavicular and mediastinal lymph nodes.[18]

Then, in the mid-20th century, as a result of awareness of the postoperative morbidities, minor modifications of Halsted's surgery were introduced by Madden and Patey, who spared the pectoralis major. Advances in hormonal therapy, radiotherapy, and chemotherapy, along with the contribution of mammography to the detection of early-stage tumours, led to the point where the management strategies for BC needed reevaluation. In the 1970s, Umberto Veronesi treated BC not bigger than 2 cm with quadrantectomy.[19] In 1955, George Crile claimed BC was not a localized disease, but rather one that spread throughout the body.[20]

In 1976, Bernard Fischer published results of his study, showing that in patients with BC, breast-conserving surgery followed by radiotherapy and chemotherapy proved just as effective in terms of survival rates as radical mastectomy. In the 1980s, he introduced an operation resembling a segmentectomy, with ALND and radiotherapy included. After 20 years of follow-up, women recruited in his study who underwent breast-conserving surgery and radiotherapy had long-term survival rates similar to those who underwent a radical mastectomy.[21]

The minimisation process in breast surgery changed the surgery of the axilla. The concept of sentinel lymph node biopsy (SLNB) was based on the existence of predictable lymphatic drainage to a regional lymph node basin and the first lymph node with the function of a filter for tumour cells. It was built on the Halsted theory, which emphasised the importance of locoregional treatment of BC due to a stepwise spread of BC. That made SLNB a staging tool for selecting candidates for systemic therapy since the SLN involvement could serve as an indicator of the distant spread of the tumour.[22] The development of SLN in BC started in the 1990s. The technical details of intra-

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18 Lakhtakia, R. (2014), e166–e169.

19 García Novoa, A.; Acea Nebril, B. (2017), Treatment of the axilla in breast cancer surgery: Systematic review of its impact on survival, *Cir Esp*, 95 (9), 503-12.

20 Caudle, A.S.; Kuerer, H.M. (2015), Targeting and limiting surgery for patients with node-positive breast cancer, *BMC Med*, 13, 149.

21 Giuliano, A.E.; McCall, L.; Beitsch, P.; Whitworth, P.W.; Blumencranz, P.; Leitch, A.M.; Saha, S.; Hunt, K.K.; Morrow, M.; Ballman, K. (2010), Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: The American College of Surgeons Oncology Group Z0011 randomized trial, *Ann Surg*, 252 (3), 426-33.

22 García Novoa, A.; Acea Nebril, B. (2017), 503-12.

operative lymphatic mapping using a vital blue dye were first described and published for melanoma in 1992 by Morton et al.[23] Two years later, Giuliano AE et al. extended the lymphatic mapping and SLNB technique to patients with BC.[24] Krag DN et al. introduced intraoperative isotope-guided SLN detection using radiolabelled colloids and the gamma detection probe.[25]

The accuracy of the method in various studies was more than 95%. It was first implemented in 1997, soon being adopted worldwide as the gold standard for axillary staging in early-stage BC. Many women with SLNs, either negative or involved with micrometastases, have since been spared unnecessary ALNDs. As a result, the reduction in ALND-related postoperative comorbidity rates and improved quality of life without affecting survival rates were confirmed by several contemporary studies.[26] Evidence that neither patients with 1 nor 2 SLNs involved with metastases benefited from ALND if radiotherapy was delivered emerged in the last decade. That further increased the number of women who were spared ALND.[27]

Conclusion

The domination of surgery in the treatment of BC patients is a two-millennia long history. Evidence that the physicians made the earliest surgical choices in BC patients of antiquity were found in the ancient texts from the 5th century B.C. to the 7th century A.D., those of Hippocratic physicians, of Archigenes of Apamea, of Galen, of Leonides of Alexandria, and Paulus Aegineta.[28] Initial treatments included invasive surgical techniques. However, it was not until the mid-19th century that breast surgery made such rapid progress with the discovery of anaesthesia and antisepsis. William Stewart Hal-

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23 Morton, D.L.; Wen, D.; Wong, J.H.; Economou, J.S.; Cagle, L.A.; Storm, F.K.; Foshag, L.J.; Cohran, A.J. (1992), Technical Details of Intraoperative Lymphatic Mapping for Early-Stage Melanoma, *Arch Surg*, 127 (4), 392–9.

24 Giuliano, A.E.; Kirgan, D.M.; Guenther, J.M.; Morton, D.L. (1994), Lymphatic mapping and sentinel lymphadenectomy for breast cancer, Ann Surg, 220, 391-401.

25 Krag, D.N.; Weaver, D.L.; Alex, J.C.; Fairbank, J.T. (1993), Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe, *Surg Oncol*, 2 (6), 335-40.

26 Thomas, J.S.; Hanby, A.M.; Russell, N.; van Tienhoven, G.; Riddle, K.; Anderson, N.; Cameron, D.A.; Bartlett, J.M.; Piper, T.; Cunningham, C.; Canney, P.; Kunkler, I.H. Supremo Trial Management Group (2017), The BIG 2.04 MRC/EORTC SUPREMO Trial: pathology quality assurance of a large phase 3 randomised international clinical trial of postmastectomy radiotherapy in intermediate-risk breast cancer, *Breast Cancer Res Treat*, 163 (1), 63-9.

27 Giuliano, A.E.; Hunt, K.K.; Ballman, K.V.; Beitsch, P.D.; Whitworth, P.W.; Blumencranz, P.W.; Leitch, A.M.; Saha, S.; McCall, L.M.; Morrow, M. (2011), Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: A randomised clinical trial, *JAMA*, 305 (6), 569-75.

28 Mannu, G.S.; Bhalerao, A. (2014), e147-8.

sted made the radical mastectomy, which included the removal of the breast, axillary lymph nodes, and pectoral muscles en bloc, which in the first half of the 20th century became the gold standard for BC treatment.[29] Over the last hundred years, with the development of hormonal therapy, chemotherapy, and radiotherapy for BC, as well as neoadjuvant chemotherapy in selected BC patients, and with established screening tools for early detection of BC, surgery in BC patients has undergone through a minimisation process. From radical, extensive surgery in BC patients a century ago, surgical treatment has turned to less invasive, safe, effective, and beneficial treatments today. Reasonable control of the disease in the majority of BC patients is now achieved with breast-conserving surgery and no ALND.[30] SLNB made possible that ALND can be avoided in women with negative SLNB, SLNs with micrometastases, as well as in those with 1 to 2 positive SLNs receiving adjuvant radiotherapy.[31,32]

Conflict of interest

All authors declare there is no conflict of interest.

29 Sakorafas, G.H.; Safioleas, M. (2009), 530-44.
30 Mannu, G.S.; Bhalerao, A. (2014), e147-8.
31 Tanis, P.J.; Nieweg, O.E.; Valdés Olmos, R.A.; Th Rutgers, E.J.; Kroon, B.B. (2001), History of sentinel node and validation of the technique, *Breast Cancer Res*, 3 (2), 109-12.
32 Giuliano, A.E.; Hunt, K.K.; Ballman, K.V.; Beitsch, P.D.; Whitworth, P.W.; Blumencranz, P.W.; Leitch, A.M.; Saha, S.; McCall, L.M.; Morrow, M. (2011), 569-75.

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Sažetak

Karcinom dojke najčešći je maligni tumor u žena. Prvi zapisi o karcinomu dojke i njegovu liječenje datiraju iz drevnog Egipta 1500 - 1600 godina pr. n. e. Terapijski pristup bolesti mijenjao se kroz povijest te je nekadašnji invazivni, kao npr. radikalna mastektomija, s vremenom zamijenjen manje invazivnim kirurškim metodama. W. S. Halsted 1894. predstavlja metodu radikalne mastektomije koja uključuje potpunu resekciju dojke, regionalnih limfnih čvorova te velikog i malog pektoralnog mišića. Unatoč čestim postoperacijskim komplikacijama, zauzimala je glavno mjesto među kirurškim modalitetima liječenja karcinoma dojke sve do 1948. kada su Patey and Dyson predstavili modificiranu radikalnu mastektomiju kojom su se, za razliku od radikalne, sačuvali pektoralni mišići te pazušni limfni čvorovi lože III, a postoperacijske su komplikacije smanjene, uz poboljšanje kvalitete života bolesnica. Ideju ograničene resekcije tkiva dojke predstavlja Veronesi 70-ih godina 20. stoljeća, nakon čega je i dalje nastavljeno smanjenje opsega i radikalnosti kiruških zahvata. Konačno, poštedna operacija dojke postaje standard u liječenju žena s ranim stadijem karcinoma dojke. Koncept biopsije limfnog čvora čuvara kod karcinoma dojke nailazi na svekoliku prihvaćenost, a njegovim usvajanjem mnoge su bolesnice pošteđene radikalnih disekcija aksilarnih limfnih čvorova, od onih čiji je nalaz biopsije limfnog čvora čuvara bio negativan do onih s mikrometastazom u istome (malim tumorskim depozitom veličine 0,2-2 mm), dok zaključci novijih studija iz posljednjih deset godina sugeriraju da se i u žena kojima je biopsijom utvrđena metastaza u jednome do dva limfna čvora čuvara disekcija aksilarnih limfnih čvorova može izbjeći bez štetnih posljedica, uz primjenu adjuvantne radioterapije.

Ključne riječi: *aksilarna metastaza, kirurgija dojke; karcinom dojke, limfni čvor čuvar*