THE ADVANCEMENT AND HISTORY OF BREAST CANCER SURGICAL THERAPY AT A GLANCE

George Dimitrov*, **George Baytchev****, **Ivan Inkov**** and **Dimitar Dimitrov**△

*Faculty of Medicine, Medical University of Sofia, Bulgaria., **Department of Thoracic Surgery, Military Medical Academy of Sofia, Bulgaria., ***Department of General Surgery, MHAT Blagoevgrad, Bulgaria.

ABSTRACT For decades now breast cancer tissue resection has been the primary method of choice for treating the disease, however this was not the case throughout the history of medicine. For centuries breast cancer was considered to be incurable via surgical approaches and that only early, low grade, lesions can be removed safely. Not until the 19^{th} century, an increase in primary surgical therapy for the disease (mainly radical mastectomies) was becoming evident due to the teachings of Morgagni, in addition to a complete re-conceivement of the etiological process of the disease by Le Dran. Currently, practitioners have achieved a very high level of proficiency in treating the disease via continuous refinement of the aforementioned facts. This resulted in tissue and organ sparing local surgical approaches, including wide local excisions through para-areolar incisions and even skin and nipple-sparing mastectomies, which have long overpassed the unnecessary and primitive high morbidity approaches performed in the earlier attempts to treat breast cancer.

KEYWORDS breast surgery techniques, breast cancer treatment, breast history

Early history of breast cancer

Currently, breast cancer (BC) surgical excision remains the gold standard for treating the disease and due to its significant social and economic impact, researchers and clinicians have attempted to identify the pathogenic processes giving rise to the disease. However it took centuries for medical practitioners to reach these conclusions. Nonetheless, even throughout the ages breast cancer has been capturing the attention of medicine and surgery practitioners universally, with the Smith Surgical Papyrus (3000–2500 b.c.) being the earliest known manuscript describing the manifestation of the disease. Despite this, the document stated that at the time "There was no treatment" for the disease [1].

Subsequently very few documents were found to contain information about breast cancer, thus only a few of the currently available medical historical manuscripts have referred to disease. Later until the 1^{st} century however, the values of early breast cancer surgery have been re-evaluated by Celsus in De Medicina, stating that; "Removal of breast tumours is futile but the early manifestations of the disease (referring to them as cacoethes), and that the majority of lesions are irritated by every method of therapy. The more violent the operations are, the more aggressive they grow" [2].

Not until the 2^{nd} century was the classical clinical observation of the disease described by Galen, stating how breast tumours resemble the crab, through comparing the limb morphological anatomy of this crustacean to the extension of deformed veins from the lesions, taking the shape of the crab's appendages. Gale went on further by mentioning that early stage disease was often possible to cure, however after a certain size was reached a cure was unattainable [3].

Moreover, Galen theorized that the disease manifested itself from black bile excess and concluded that local excision and therapy could not cure the systemic imbalance giving rise to this pathological formation. Galen's theories dominated until

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[1]George Dimitrov, Faculty of Medicine, Medical University of Sofia, Bulgaria, george121@gmail.com

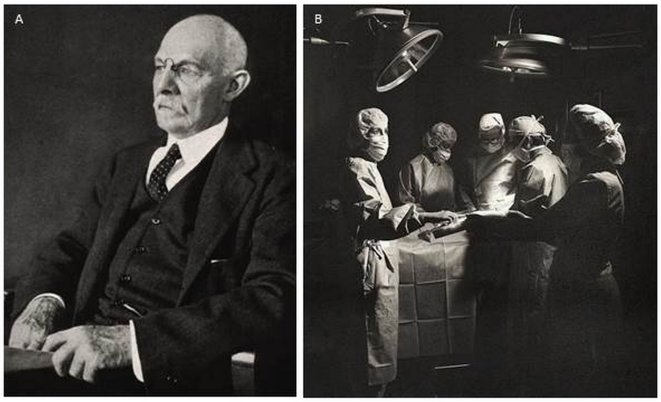

Fig 1. William Stewart Halsted (1852-1922) a pioneer in surgical therapy and father of modern breast surgery (A). Halsted and his medical team at Johns Hopkins University Hospital in Baltimore, performing a radical mastectomy (B) [8].

the renaissance, until 1652 in which the description of breast cancer and the etiology of the disease had further taken several steps in the wrong direction, through Tulp's introduction of the disease being contagious and passed from person to person via describing this phenomenon in a single documented incident (N. Tulp, Observationes medicae 1652)[4]. This misconception was accepted as conclusive evidence and would last well into the 20^{th} century among some people.

Early advancements in treatment modalities

The frequency of surgical therapy, including some early forms of mastectomy and dissections of axillary lymph nodes, has started to increase with teachings from Morgagni. During the information age which, lasted until the 19^{th} century, practitioners such as Le Dran, abandoned Galen's systemic pathology and completely replaced the etiology by a more credible cellular pathological hypothesis, which was first adopted by Virchow. As a result, Le Dran suggested that breast cancer should be considered as a local disease which is able to spread throughout the body by hijacking the body's own lymphatic system thus remnants of the disease could be found in the axilla. Following this, operation undertaken on women with breast cancer, not only was the primary lesion with adjacent tissue readily removed, but also enlarged axillary nodes [5].

Axillary clearance was further supported by a British surgeon by the name of Moore during the 19th century. He adopted and highlighted the necessity of a total breast resection in women with cancer, in addition to removal of axillary nodes in case of evident and palpable enlargement [6].

The latter was further expanded in 1877 during which axillary clearance was suggested and accepted as a routine procedure in BC, even if evident lymphadenopathy was lacking. The pinnacle of breast cancer surgical treatment of that era culminated with the introduction of the radical mastectomy as proposed by Halsted & Meyer in 1894. Using this approach, these surgeons demonstrated enhanced regional disease control as a result establishing this method as the gold standard treatment choice of the era [7].

Moreover, they supported total axillary lymph node dissection (ALND) of levels I, II and III, with readily dissecting N. thoracodorsalis and N. Thoracicus longus alongside the axillary contents through removal of the Pectoralis minor and major muscles. Currently however, the Halstedian **(Fig 1.)** approach has been succeeded by less extensive surgeries and today it is used quite rarely only for locally advanced tumors directly involving the muscle, or when down-staging could not be achieved by chemotherapy.

During the mid-20^{th} century, the various signs observed in BC patients had started to be taken into account. By 1943 Haagensen & Stout had described the signs observed in the majority of patients: breast skin edema w/wo ulceration, chest wall fixation, fixed axillary nodes and nodal enlargement (<2.5cm). 42% local recurrence rate was given to women who presented with two or more signs, in addition to a very low 2% five-year disease-free survival rate [9].

In spite of these findings at the time, radical surgery was declared as an insufficient treatment for patients presenting these signs.

The modified Radical, Skin-sparing and Nipple-sparing mastectomies

During the 1970s, a transition was seen in the treatment of advanced operable breast cancer, which involved the adoption of Patey & Dyson's suggested modified radical mastectomy approach thus replacing the Halstedian radical approach [10].

This resulted due to the observations that: (1) advanced local disease patients and those presenting Haagensen's signs reporting were diminishing in number, (2) removal of the pectoralis major muscle was unnecessary in local control of early stage disease based on the TNM classification [11] (stage 0, 1-2), (3) neither method was able to achieve replicable complete local regional control in stage IIIa or IIIb breast cancer, however Patey's was a more conserving approach. Hence the modified radical mastectomy method only incorporated the removal of the breast parenchyma (~90%) and surrounding tissue in addition to level I-III of axillary nodes, through extirpation of the pectoralis minor muscle and without resection of the pectoralis major muscle. Moreover, with the addition of radiation therapy in local disease treatment significant improvements were seen in the cancer regional control with several studies supporting these observations [12,13]. Generalized treatment pathways for both subtypes of stage III tumours can be seen in **Fig 2.**

Currently the most common form of mastectomy performed in patient presenting with Tis-T3 tumours is the skin sparing mastectomy [15,16], which involves removing all breast tissue, the nipple-areolar complex, cicatrices of previous breast surgical procedures, interpectoral fascia and appropriate axillary lymph node investigation - ALND (lvl I-II) or a sentinel node biopsy, thus sparing both the pectoral muscles in addition to N. Thoracicus longus and N. Thoracodorsalis. This approach has demonstrated a recurrence rate of less than 7% in contrast to the long-term rate obtained by using the classical modified radical mastectomy [17]. Over the last decade, the nipple-sparing mastectomy (NSM) and the prophylactic subcutaneous mastectomy have been gaining significant attention as a treatment for early-stage breast cancer patients, particularly since a risk-reducing operation in high-risk patients (i.e. BRCA1/2 carriers). Currently, both methods are used only when immediate reconstruction of the breast is planned, and the most important factor used in judgment of preservation of the nipple in NSM is the intraoperative frozen section analysis of the subareolar tissue [18]. Key points describing the eligibility of the cancer patient to undergo primary surgery can be found in **Table 1**, some of

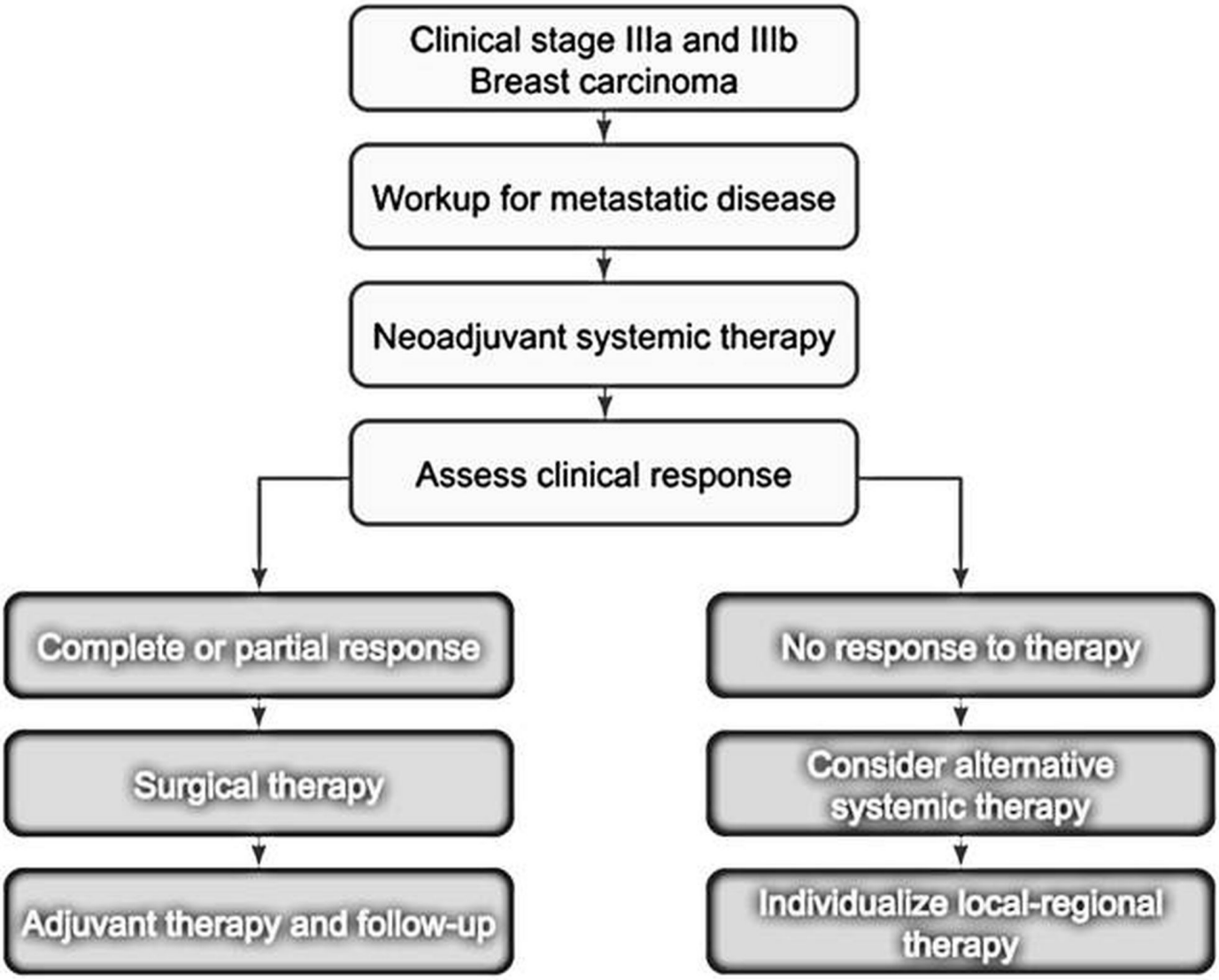

Figure 2:Treatment pathways for stage IIIA and stage IIIB BC. Schematic adapted from Schwartz' Principles of Surgery 10th ed [14].

the described contraindications can be down-staged by systemic and/or local neoadjuvant therapies.

Table 1. Concise eligibility factors of the cancer patient undergoing the surgical procedures described in this paper; Radical mastectomy (Halsted), modified radical mastectomy (Patey), Skin-sparing mastectomy, Nipple-sparing mastectomy and breast conserving surgery (lumpectomy); the most common breast operation currently performed (70% of BC cases). *currently best mastectomy treatment option if the extent of the disease allows it. Not only does it provide very low recurrence rates similar to modified radical mastectomies, but also allows complete breast reconstruction and thus better esthetic results than the ones observed in skin-sparing mastectomies. BC- Breast cancer, RT- Radio Therapy, Tis- in situ tumour.

Breast conserving surgery

The next evolution in treating the disease via surgical management came with the introduction of organ conserving therapy. It was initially reported in 1937 by Geoffrey Keynes of St Bartholomew's Hospital, London. Mr. Keynes also suggested the incorporation of radium treatment alongside the surgical excision as previous cases have shown a better response and regional disease control [19]. Nonetheless, several follow-up studies have demonstrated that there was an insignificant difference between the patients whom had undergone total mastectomy, breast conserving lumpectomies (wide local excisions) or WLE with radio therapy (RT) in regards to both disease free and overall survival [12,20]. However it was evident that the omission of radiation therapy had a significant impact on the ipsilateral disease recurrence rate in patients whom had undergone WLE alone. Despite this fact breast conserving therapy has achieved an unchallengeable status in BC treatment and is currently the standard treatment routine performed in patients with early stage disease. The approach itself involves resection of the primary tumor in addition to a margin of normal appearing breast tissue **(Fig 3)**.

Moreover, an axillary lymph node status assessment and adjuvant radio-therapy is often incorporated. This method is preferred over total mastectomy as it not only spares removal of

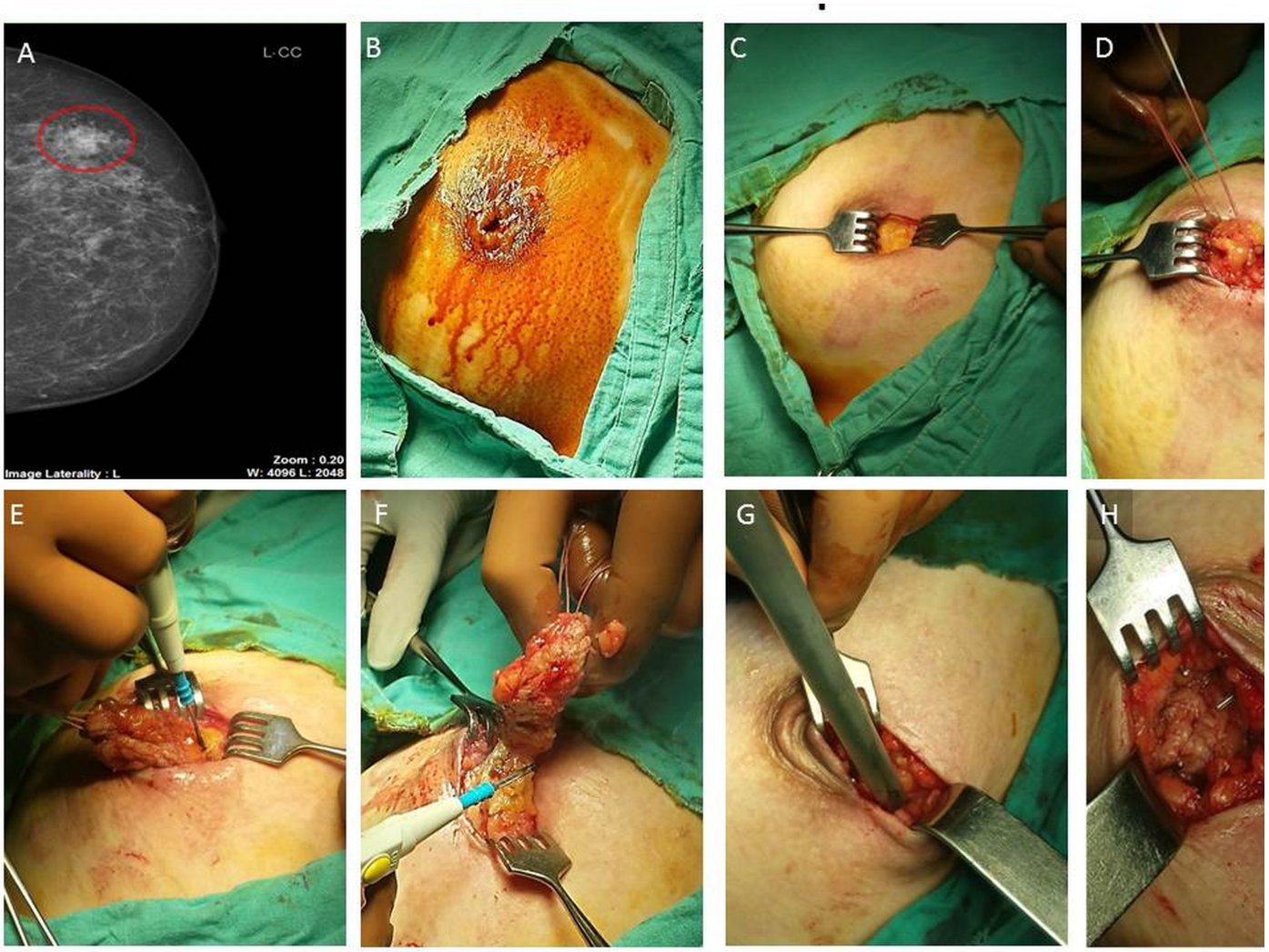

Figure 3 Lumpectomy procedure performed at GH Blagoevgrad, Bulgaria. The 54 year old patient presented with a suspicious mass turning out to be an early invasive breast cancer (stage 2; T2 N0 M0) on the left breast, while undergoing mammographic screening and subsequent ultrasonography (A). During the surgery a curvilinear para-areolar incision above the palpable lesion was made, thus allowing access to the deeper tissues (B-C). In order to enhance control the tumour was fixed using a suture (D) and excised with some normal appearing tissue margins using electrocautery (E-F). Finally the region was marked using stainless-steel clips allowing better localization of the area in case of follow up radio-therapy (G-H).

the whole breast, pectoralis muscles and level III lymph nodes if axillary assessment is required, but also has demonstrated survival rates equivalent to total mastectomy in addition to faster patient recovery [21,22]. The only inconvenience of this type of approach is that the surgeon is completely responsible to ensure total tumour excision. If the subsequent histopathological analysis shows that no clear margins were obtained according to the currently accepted standard (no tumor on the ink), re-operations must be performed until these criteria are met. This in turn will minimize the risk of local recurrence in addition to reducing the probability of re-excisions without compromising the local control, especially due to the recent undertaking of the "no tumour on ink" criteria described in the SSO-ASTRO consensus guidelines [23]. Unfortunately in regards to in situ disease (DCIS), controversy still exists among specialists in defining optimal margins as of this writing [23,24]. Overall, breast conserving surgery is indicated in any patient with favorable tumor - to - breast size ratio (i.e. tumour size/breast size ratio) that allows lumpectomy, without compromising the cosmetic outcome. Generally there is no cut-off point for tumor size as long as the size of the breast allows conservation.

Oncoplastic surgery

As previously mentioned, breast conserving surgery has become the primary treatment option for women with BC, with several subsequent clinical trials demonstrating equivalent outcomes in terms of disease free and overall survival rates between WLE with radiotherapy and mastectomy [12,13]. Nonetheless, despite the favorable results obtained from these methods, a cosmetic defect was unfortunately unavoidable in some of the cases thus affecting the patient's symmetry and image. As a result the utilization of oncoplastic surgery has started to gain favourable attention since its first recommendations in 1994 including the ones from Werner Audretsch. This approach is utilized in order to repair breast imperfections caused by partial mastectomies, by combining both volume reduction in addition to immediate flap reconstruction techniques [25]. Moreover, both the indica-

Table 1

Procedure	Indications	Absolute contraindications for surgery
Radical Mastectomy	Extensive tumour invasion into pectoralis muscles, and/or chest wall. Neoadjuvant therapy is not effective.	**Systemic:** Distant metastasis, frail and/or very old patient, cachexia, organ dysfunction (i.e., cannot tolerate surgery)
		Local: Peau d'orange skin, significant breast edema,inflammatory carcinoma, confirmed supraclavicular lymph node metastasis, ipsilateral edema of the upper limb, confirmed pathological enlargement of parasternal lymph nodes.
Modified Radical Mastectomy	Malignant tumour Tis-T3, multifocal disease, Persistent positive margins after multiple resections, history of RT.	See above – neoadjuvant therapy, recommended
Skin-sparing mastectomy	Malignant tumour Tis-T3, skin is needed for, reconstruction, small breast size.	Peau d'orange skin, significant breast edema, inflammatory carcinoma or any other invasion of skin by cancer.
***Nipple- sparing mastectomy**	Tumour distance not less than 2-3cm from the areolar border, small breast, no prior breast,surgeries.	Cancer involving the skin and nipple, paget's disease, large pendulous breast, extensive ptosis and/or extensive advanced disease, bloody discharge.
Breast conserving surgery	Stages Tis-T3, overall favorable tumor size-to-breast size ratio.	Stage IV disease

tions and contra-indications for undergoing this type of surgery are the same as the ones for breast conserving surgery in addition to better cosmesis. Currently oncoplastic surgery may refer to several different reconstructive approaches of the breast after tumour excision, however initially oncoplastic surgery was used to describe a partial mastectomy in conjunction with a breast reconstruction involving the formation of a large myocutaneous flap using either the M. Rectus Abdominis or M. Latissimus Dorsi [26]. The most widely used oncoplastic methods performed today include: batwing mastopexy lumpectomy, round block mastopexy lumpectomy, parallelogram mastopexy lumpectomy, reduction mastopexy lumpectomy, lateral segmentectomy lumpectomy, and the central lumpectomy [26,27]. **Table 2**, provides a brief explanation of the advantages of each of the methods.

Table 2. Concise information on the advantages of the various oncoplastic surgical methods: batwing mastopexy lumpectomy, round block (donut) mastopexy lumpectomy, parallelogram mastopexy lumpectomy, reduction mastopexy lumpectomy, lateral segmentectomy lumpectomy, and the central lumpectomy [28].

Staging and therapeutic values of axillary surgery

As previously mentioned, axillary clearance has been incorporated in BC surgical treatment since the era of Halsted. Interestingly, when ALND was first proposed, it was for therapeutic purposes however it soon became clear that the majority of woman who had presented with nodal involvement died of BC after undergoing local surgical therapy alone. As a result currently nodal assessment is utilized only for diagnostic, staging procedures to determine the extent of the disease **(Fig 4)** [16].

Unfortunately, for a significant number of patients with BC, the nodal involvement cannot be accurately predicted based on the characteristics of the primary lesion alone. In addition the ALND itself presented with a high morbidity and increased risk

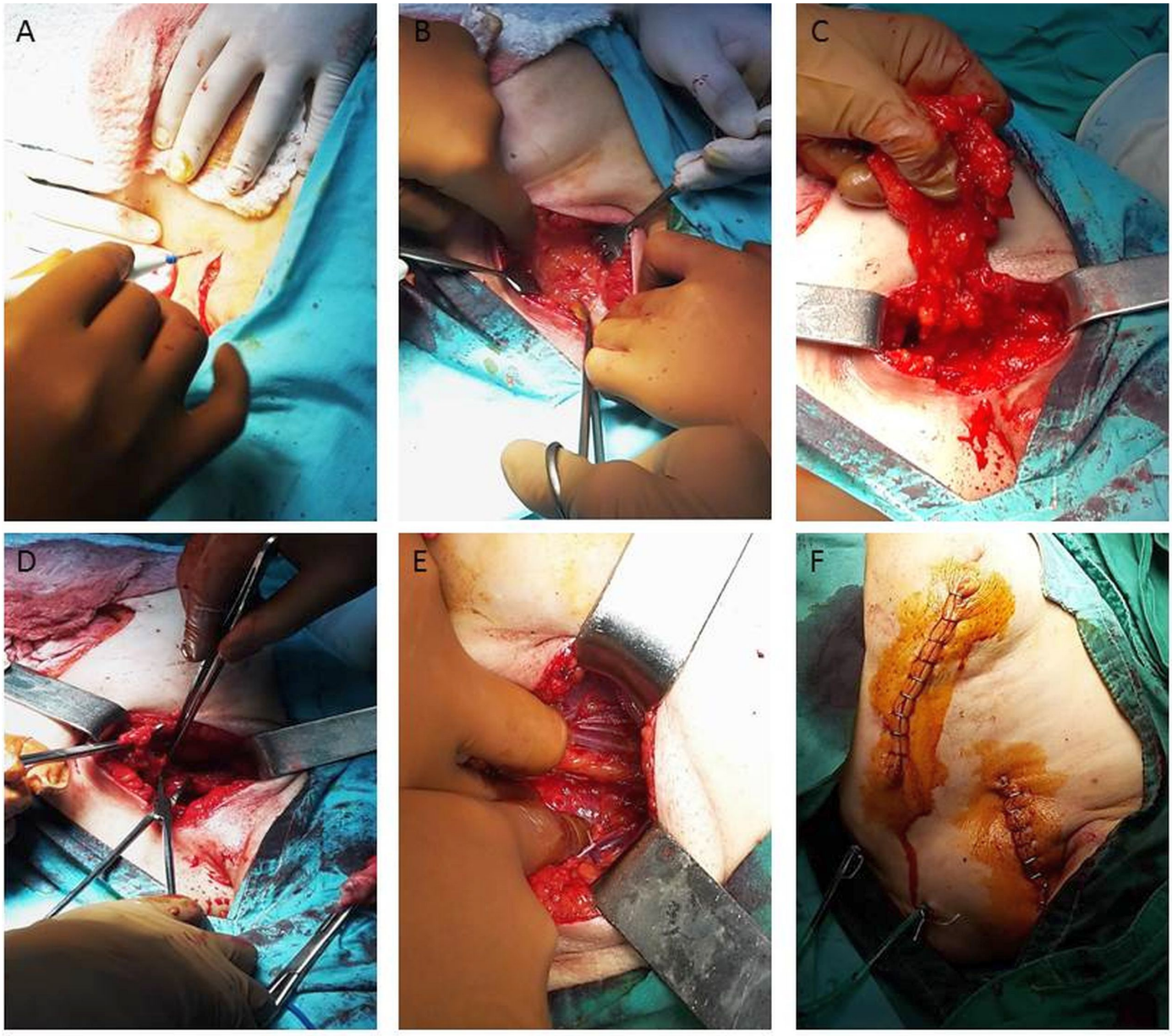

Fig 4. Axillary lymph node dissection (ALND) performed at GH Blagoevgrad, Bulgaria – The 60 year old patient presented with a Stage II disease (T2 N1 M0) hence an axillary clearance (lvl I-II) alongside WLE was warranted. Unlike in mastectomy where the removal of the breast allows access to the axillary contents, a separate transverse incision was made over the axillary fossa (A). The axillary content was then liberated and excised until reaching the borders of the axillary fossa; medially M. Serratus anterior, Posteriorly M. Subscapularis, laterally M. Latissimus Dorsi and superiorly the inferior border of the axillary vein (B-C). Leftover tissue was removed, completely clearing lvl I-II with sparing N. Thoracodorsalis and N. Thoracicus Longus (D-E). Finally, a Hemovac drainage system was installed and the axilla was closed using an interrupted sub-cutaneous suture, while the skin with stainless steel clips (F).

Table 2

Procedure	Advantage
Batwing mastopexy lumpectomy	Used when the cancer is adjacent to or deep to the nipple (without direct involvement), lumpectomy can be performed without sacrifice of the nipple itself.
Round Block mastopexy lumpectomy	Best used for segmentally distributed cancers located in the upper or lateral breast to achieve resection of long, narrow segments of breast tissue.
Parallelogram mastopexy lumpectomy	The most primary oncoplastic technique involves removal of the skin island located directly superficial to the known disease and is most commonly used for superior pole or lateral cancers.
Reduction mastopexy lumpectomy	Used when cancers are located in the lower pole of the breast, traditional lumpectomy using curvilinear incision may result in unacceptable down-turning of the nipple due to scar contracture after radiotherapy.
Lateral segmentectomy lumpectomy	A variation of the parallelogram lumpectomy, the lateral segmentectomy is especially useful for lesions located within the lower breast, including the 3 o'clock and 9 o'clock positions.
Central lumpectomy	Although central lumpectomy removes the nipple and underlying central tissues, it typically leaves behind a significant breast mound.

of axillary seroma and lymphedema among other possible complications. However, with the introduction of the low morbidity sentinel lymph node (SLN) biopsy, came a reliable, convenient and accurate identification method of patients with nodal involvement [29]. The actual method itself involves investigating the first lymph node that drains the area of the occupying tumour. Generally a Lymphazurin blue dye is utilized for the lymphatic mapping, but other agents such as the radioisotope (RI) technetium can be used instead or synergistically with the dye [30]. Studies have shown that surgeons can identify the SN in 95% of the cases when incorporating both techniques (~75% accuracy if used individually), thus further allowing evaluation of the remaining nodes in 90% of these cases (89% sensitivity and 94% specificity) [31]. As previously mentioned the morbidity of SLN biopsy is much lower than the one obtained from ALND, however the latter procedure is warranted when nodal involvement has been confirmed using SN or in cases that SN biopsy is contraindicated [32]. It has been shown that in 95% of the patients, nodal involvement can be accurately identified solely by excision of nodes from level I-II. In addition according to further observation isolated metastases to level II are quite uncommon. Thus, unlike in Halsted and Patey's approaches, currently only levels I and II are dissected for evaluation, with level III excision reserved for patients with gross nodal involvement [33]. All the major guidelines currently used in nodal assessment are based on three extensive clinical trials [32,34,35]. These studies demonstrated that in selected patient with up to 2(+) SLNs, who are undergoing WLE followed by radiotherapy and systemic treatment, further axillary clearance is not absolutely indicated and can be safely omitted. Furthermore, novel detection methods have recently attracted the attention of practitioners by demonstrating much higher detection rates. An example may be the utilization of indocyanine green (ICG) with fluorescence which have demonstrated easier and rapid identification of SLN, in contrast to using RI alone [36]. Another example is the use of supermagnetic iron-oxide with magnetic tracer, which has also demonstrated elevated detection rates [37].

Conclusion

Breast cancer surgical treatment and therapy in general has gone a long way since it has been initially described in Smith's surgical papyrus. Currently tumours are classified by molecular subtyping obtained via immunohistochemistry or genetic and molecular profiling. This subtyping has proved to be a practice changing factor in local and systemic treatment decision making in addition to risk stratification. The significant treatment advances in breast cancer is a result of multidisciplinary team approach including surgery, radiotherapy, chemotherapy, hormonal and target treatment when indicated. Generally, surgeons are the first physicians consulted by the BC patient, hence it is crucial for these doctors to be well prepared in all aspects relating to the breast. As a result, optimal outcomes for patients will not be that far to reach.

Authors' Statements

Competing Interests

The authors declare no conflict of interest.

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