The Official Journal of the Hellenic Senologic Society

Mastologia

December 2020

EDITORIAL

ARTICLES

The Official Journal of the Hellenic Senologic Society

Mastologia

CENTRE OF PSYCHOSOCIAL SUPPORT FOR WOMEN WITH BREAST CANCER "ELLI LAMBETI"

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The Centre "ELLI LAMBETI"

The Centre of Psychosocial Support for Women with Breast Cancer "Elli Lambeti" was founded in April 2002 by the Hellenic Senologic Society with the aim to improve the quality of life of women with breast cancer and at the same time support the members of their families. It is an independent non-governmental Centre which is sponsored by public and private entities.

Since its creation until today, the Centre has offered its services to over 4500 people, who either visited it, or asked support via phone conversations either because they live in rural areas, or because they are not able to move, or even due to their wish to remain anonymous.

In the friendly and pleasant environment of the Centre, trained psychologists provide psychological services and social support by appointment for FREE, following the principles of medical confidentiality.

To whom the Center refers to

- All women with a recent diagnosis of breast cancer
- All women diagnosed with breast cancer and who follow medical treatment
- All women who are in the process of recovery
- All close family members as well those persons who are close to their work and social environment
- All women with carcinophobia

Services offered by the Centre.

The Center offers the following services free of charge:

- Information in relation to the disease
- Individual psychological and counseling support to women with breast cancer
- Psychological and counseling support to their family members, both during and after treatment
- Support the process of reintegration into the family and the work environment
- Ability to meet and contact other women facing the same problem
- Participation in cultural events and other activities (meetings, celebrations, bazaars, concerts,drawing exhibitions etc.)
- Group therapy
- Beauty therapeutic groups
- Dietary therapeutic groups
- Provision of specialised brochures

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CONTENTS

New edition

EDITORIAL

ARTICLES

Welcome note

Dear Colleagues, Dear Friends,

It is a different thing to desire to do something and a different thing the reality with a heavy workload, especially during this difficult period of time that humanity is going through the pandemic of the COVID19.

For this reason and in order for the seamless publication of our electronic Journal "Mastologia" of the Hellenic Senologic Society's in English to continue, I have asked our colleague Dr Vassilios Georgountzos to undertake the Chief Editor position of the Journal and personally stay as Deputy Editor in Chief.

I would like to thank Dr Georgountzos for his acceptance and hope to have a harmonic and fruitful collaboration.

Lydia Ioannidou-Mouzaka MD, PhD

Ass. Professor, University of Athens Medical School
Gynecologist-Surgeon-Senologist,
National Representative of Greece in the
European Committee Initiative on Breast Cancer
Representative of the Hellenic Medical Association in
UEMS for the needs in Breast Cancer Surgery
President, Hellenic Senologic Society
Director, Hellenic School of Senology

Dear Colleagues,

I would like to thank the President of the Hellenic Senologic Society (HSS) and former Chief Editor of the Journal "Mastologia", Prof. Lydia Ioannidou-Mouzaka and the Members of the Board of Directors of the HSS for the honor to trust me with the Edition of the Journal and select me as the Chief Editor.

I appreciate very much that Pr Mouzaka accepted to stay as Deputy Director in Chief of the Journal.

The Journal "Mastologia" publishes scientific papers from the field of Senology and all the relative scientific fields. The republication of the Journal in this issue coincides and includes pictures of the 40 years anniversary of the Society.

During its 40 years life, the HSS has been providing scientific and social work all around Greece.

Dr Vassilios Georgountzos MD, PhD

Chief Editor,
Radiologist, Coordinator Director of Breast Imaging
and Radiology Department of the State General
Hospital of Athens "George Gennimatas"
p. Director of the Hellenic School of Senology

Greetings from the President of the Hellenic Senologic Society (HSS) for the Celebration of the 40-year Anniversary of the HSS and the edition of the corresponding book

Lydia Ioannidou-Mouzaka MD, PhD
Ass. Professor, University of Athens Medical School
Gynecologist-Surgeon-Senologist,
National Representative of Greece in the ECIBC
for Breast Cancer Screening and Breast Centers
Representative of the Hellenic Medical Association in UEMS
for the needs in Breast Cancer Surgery
President of the Hellenic Senologic Society
Director of the Hellenic School of Senology

To celebrate the 40 years anniversary of the scientific and social contribution of the Hellenic Senologic Society, it was decided and published a Yearbook for its 40th year of contribution. This book reflects the scientific development of Senology in Greece, including the scientific programs with the names of the speakers of the 14 Panhellenic Senologic Congresses and the 3 Internationals that were organized during these years.

In my greeting I also mention all the actions of the Society during these years. The following people had the kindness to preface the book:

1) Archbishop of Attica and Greece Mr Ieronymos B'

2) The Sexologist, Ass. Professor of Obstetrics and Gyne cology at UoT, Dr Zisis Papathanasiou, who was the one who inspired me to specialize in Senology.

3) Dr Domique Gros Radiologist-Senologist, son of my Professor Charles Marie Gros, with whom we worked together for two years in Strasbourg

4) Dr Edio Pusterla, Gynecologist Senologist, Founder of the Swiss Senologic Society, with whom we specialized in Strasbourg

5) Dr Mauricio Magalhaes Costa, current Pesident of the SIS and a member of the National Medical Academy of Brazil.

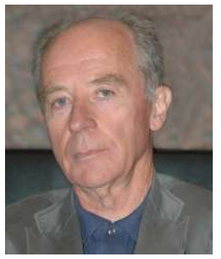
Also distinguished colleagues from each related specialty with Senology prefaced the Book:

- For the field of Pathology, emeritus Professor and former Dean of UoA and former Minister of Health Dr Christos Kitas
- For the field of Radiology, the Professor emeritus of Radiology, Director of the Imaging and Interventional Radiology Unit of IASO, Dr Dimitrios A. Kelekis
- For the field of Medical Oncology the Medical Oncologist, emeritus Professor at UoA, Dr Constantin Gennatas
- For the field of Plastic Surgery, the Colleagues, Dr Apostolos Mandrekas, Plastic Surgeon, Ret. Captain of the Hellenic Navy and Director of ARTION Plastic Surgery Center and Dr Dimitrios Chapsas, Ret. Commander
- And for the field of Clinical Genetics the Clinical Laboratory Geneticist nd Director of ALab Genetics and Genomics Center, Dr Lina Florentin.

THE BOOK IS PREFACED BY

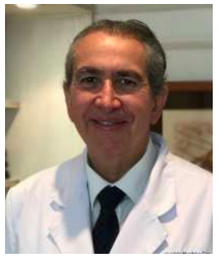
The Archbishop
of Athens and all Greece
Mr Ieronymos B'

Zissis Papathanasiou MD, PhD
Sexologist,
Ass. Pr of Obstetrics and Gynecology,
Aristotle University of Thessaloniki

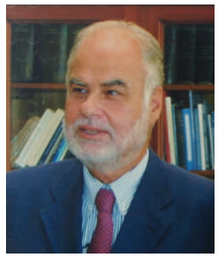


Dominique Gros MD
Radiologist-Senologist,
Doctor of the University of Strasbourg

Edio Pusterla MD
Gynecologist-Senologist,
Director of Senologia Department Ticcino



Mauricio Magalaes Costa MD
Plastic Surgeon,
President of Senologic International Society (SIS),
Member of the National Academy of Medicine Brazil



Christos Kittas MD PhD
Pathologist,
p. Minister of Health,
p. Rector of the University of Athens,
Emeritus Prof. of Pathology of the University of Athens
Director of Pathology Department of Bioiatriki

Dimitris Kelekis MD, PhD, EBIR
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Constantin Gennatas MD, PhD
Medical-Oncologist,
Emeritus Pr of University of Athens

Apostolos Mandrekas MD, PhD
Plastic Surgeon, Captain(ret.) Hellenic Navy
p. - President Hellenic Society of Plastic,
Reconstructive and Aesthetic Surgery
Director ARTION Plastic Surgery Center

Dimitris Chapsas MD
Plastic Surgeon, Commander (ret.) Hellenic Navy
former Member of the BoD of the HSS

Lina Florentin, B.Sc.,PhD,ErCLG
Clinical and Laboratory Genetisist,
Director of Alpha Lab Center of Genetic and Genomic

The Anniversary Yearbook of 40 consecutive years of operation of the Hellenic Senologic Society (HSS)

The Board of Directors of the Hellenic Senologic Society (HSS), offered “Honoris Causa”, its anniversary Yearbook of 40 consecutive years of operations to known Greek personalities of the scientific, political, religious and social fields. This book includes the contribution of the HSS to the social and scientific fields of Greek Society. The following photos show the meetings that the Board Members had with the honored persons.
Unfortunately, due to the current situation of the well-known problem that humanity experiences world-wide caused by Covid-19, we were not able to keep all the meetings we had planned. It wasn’t possible to meet with all the people of the State and Political Leadership and of the Religious, Scientific, and Social community of our Country.

The Anniversary Yearbook was given to the S.A. President of the Hellenic Republic Mrs Katerina Sakellaropoulou.

With this opportunity we would like to inform you, that the “21st SIS World Congress on Breast Cancer and Breast Health Care” organized by Senologic International Society (SIS) in Greece in collaboration with the HSS is under the Auspices of the President of the Hellenic Republic Mrs Katerina Sakellaropoulou, as well as, under the Auspices of His All Holiness the Ecumenical Patriarch Mr. Vartholomeos 1st.

With S.A. the President of the Hellenic Republic Mr Prokopis Pavlopoulos, the President of the Hellenic Senologic Society Pr Lydia Ioannidou-Mouzaka, the Vice President of the Society Dr Vasileios Barbounis, the General Secretary Dr Politimi Leonardou and the Treasurer Dr Georgios Kokkalis.

With the Archbishop of Athens and all Greece Mr Ieronymos B' and the President of the HSS Pr Lydia Ioannidou-Mouzaka together with the General Secretary of the 21st SIS World Congress on Breast Cancer and Breast Health Care, Dr Konstantina Papalla and the HSS secretary Lydia Assoniti.

In the context of the completion of the briefing of the Political, Religious and Political Leadership of our Country and despite the current political and social problems and the absence of the Prime Minister Mr Kyriakos Mitsotakis in Brussels, the Commemorative-Anniversary book of the HSS for its 40th year operation, which was intended for the Prime Minister, was received by the Parliament Member of Chania, of ND, Mrs Dora Bakoyannis.

With the same pleasure, the Representatives of HSS offered the commemorative book to Mrs Bakoyannis herself, in which the relevant information was made for the realization of the goals set by HSS and the steady growth of our efforts within the current structure of the Health System.

Her knowledge and interest in the developed topics surprised the attending Members of the Board of Directors of HSS

With the Vice-President of the European Commission Mr Margaritis Schoinas and the President of the HSS Pr Lydia Ioannidou-Mouzaka.

With the President of the Greek Political Party SYRIZA and former Prime Minister of Greece Mr Alexis Tsipras, the Parliament Member and Head of the Parliamentary Group of SYRIZA the physician Dr Olga Gerovassili, the President of the HSS Pr Lydia Ioannidou-Mouzaka and the Chief Editor of the Medical Journal “Mastologia” and p. Vice-President of the HSS Dr Vassilios Georgountzos.

With the President of the Greek Political Party KINAL Mrs Fofi Gennimata, the President of the HSS Pr Lydia Ioannidou-Mouzaka and the Treasurer of the HSS, Dr Georgios Kokkalis

With the General Secretary of the Communist Greek Party KKE, Mr Dimitris Koutsoumbas the President of the HSS Pr Lydia Ioannidou-Mouzaka, the Vice President Dr Vassilios Barbounis and the Treasurer Dr Georgios Kokkalis.

With the President of the Greek Political Party “Enosi Kentroon” Mr Vassilis Levendis, the President of the HSS Pr Lydia Ioannidou-Mouzaka and the p. Vice-President of the HSS and Chief Editor of the Medical Journal “Mastologia” Dr Vassilios Georgountzos

With the A' Vice President of the Greek Parliament and Physician Dr Nikitas Kaklamanis, the President of the HSS Pr Lydia Ioannidou-Mouzaka and the Treasurer of the HSS Dr Georgios Kokkalis.

With the Minister of Justice and Physician Dr Constantinos Tsiaras, the President of the HSS Pr Lydia Ioannidou-Mouzaka, the Chief Editor of the Medical Journal "Mastologia" and p. Vice President of the HSS Dr Vassilios Georgountzos.

With the Minister of Health and Social Affaires of Greece, Physician Dr Vassilios Kikilias and the President of the HSS Pr Lydia Ioannidou-Mouzaka

With the Minister of Labour and Social Affairs, Mr. Constantinos Hatzidakis, and the President of the HSS Pr Lydia Ioannidou-Mouzaka.

The President of the HSS Pr Lydia Ioannidou-Mouzaka, is offering the 40 years anniversary Yearbook to Dr Marietta Giannakou, former Minister of Health and Social Affaires, former Member of the European Parliament, Physician and Member of the Greek Parliament.

With the Regional Governor of Attica and Physician Dr Georgios Patoulis, the President of the HSS Pr Lydia Ioannidou-Mouzaka, the Chief Editor of the Medical Journal “Mastologia” Dr. Vassilios Georgountzos, the Secretary General of the 21st SIS World Congress on Breast Cancer and Breast Health Care Dr Konstantina Papalla and the Board Member of the HSS Dr Christina Tsionou

With the Regional Governor of Larissa, Mr Athanasios Agorastos and the President of the HSS Pr Lydia Ioannidou-Mouzaka

With the Major of Athens Mr Kostas Bakogiannis, the Deputy Major of Health and Physician Dr Theodoros Kalampokas, the President of the HSS Pr Lydia Ioannidou-Mouzaka and the Secretary General of HSS Dr Politimi Leonardou.

With the Medical Oncologist and Rector of University of Athens Pr Athanassios-Meletios Dimopoulos, the President of the HSS Pr Lydia Ioannidou Mouzaka and the Chief Editor of the Medical Journal “Mastologia” Dr Vassilios Georgountzos.

With the President of the Medical School of Athens Pr Petros Sfikakis, the President of the HSS Pr Lydia Ioannidou-Mouzaka and the Treasurer Dr George Kokkalis .

With the President of the Hellenic Medical Association, Dr Georgios Patoulis, the President of the HSS Pr Lydia Ioannidou-Mouzaka, the Chief Editor of the Medical Journal "Mastologia" Dr. Vassilios Georgountzos, the Board Member Dr Christina Tsionou and the Secretary General of the 21st SIS World Congress on Breast Cancer and Breast Health Care Dr Konstantina Papalla.

With the President of the Senologic International Society (SIS), Pr Mauricio Maghalaes Costa, together with his wife and the President of the HSS Pr Lydia Ioannidou Mouzaka.

With the President of Doctor's Association of Piraeus and Athens, Dr Matina Pagonis and the President of the HSSociety Pr Lydia Ioannidou Mouzaka and the Chief Editor of the Medical Journal "Mastologia" Dr Vassilios Georgountzos, together with his wife, High School Teacher Mrs Christina Alevizou.

With the Metropolitan of Rhodes Mr Kyrillos and the President of the Hellenic Senologic Society Pr Lydia Ioannidou-Mouzaka

With the Metropolitan of Dimitriados and Almirou Mr Ignatios, who had the kindness to visit, as an act of courtesy, the Doctors who examined voluntarily at Anatoli, Larisa (see last picture) .
The President of the HSS Pr Lydia Ioannidou-Mouzaka, and the Chief Editor of the Medical Journal "Mastologia" Dr Vassilios Georgountzos.

With the Metropolitan of Messogaias and Lavreotikis Dr Nikolaos, the President of the Hellenic Senologic Society Pr Lydia Ioannidou-Mouzaka, the Treasurer Dr Georgios Kokkalis and the Chief Editor of the Medical Journal "Mastologia" Dr Vassilios Georgountzos.

With the Metropolitan of Amaroussiou, Kifissias and Oropou, Mr Kyrillos, the President of the Hellenic Senologic Society Pr Lydia Ioannidou Mouzaka, the General Secretary Dr Polytimi Leonardou, the Chief Editor of the Medical Journal "Mastologia" and Vice President of the Society Dr Vassilios Georgountzos.

With Metropolitan of New Ionia, Filadelphias and Chalkidonos, Mr Gavriil, the President of the HSS Pr Lydia Ioannidou-Mouzaka, the Chief Editor of the Medical Journal "Mastologia" Dr Vassilios Georgountzos and the Medical Journalist Mr Michalis Gkagkogiakis.

With the Metropolitan of Larisa and Tirnavos, Mr Ignatios, the Parliament Member of Karditsa of ND Mrs Assimina Skondra and the President of the HSS Pr Lydia Ioannidou-Mouzaka.

With the Metropolitan of Dimitriados and Almirou Mr Ignatios, who had the kindness to visit, as an act of courtesy, the Doctors of the HSS who examined voluntarily -free of charge- at Anatoli, Larisa accompanied by the Father Rizos Komitsas, the President of the HSS Pr Lydia Ioannidou-Mouzaka, the General Secretary Dr Polytimi Leonardou and the Treasurer Dr Georgios Kokkalis.

Lastly we would like to mention, that two Members of the BoD of the HSS, Pr Antigoni Poultsidou (photo) and Dr Alexandros Asimakis (photo), couldn't be present in the meetings that took place, because they are living in another cities, away from Athens.

Breast Lymphomas: A Pathological Approach

Eleftheria Lakiotaki[1], Penelope Korkolopoulou[1], Christos Kittas[2]
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Abstract

Objectives: Breast involvement by lymphoma is rare, either as primary site (2,2% of extranodal lymphomas) or as secondary involvement by systematic disease. The aim of this review is to comprise a synoptic presentation of primary breast lymphomas, including new entities associated with breast implants, and lymphomas disseminating to the breast with emphasis in recording different histological subtypes and their special characteristics.

Methods: We reviewed all relevant published reports extracting information about the pathology of lymphomas involving the breast and important attributes regarding presentation, pathogenesis, genetic features and therapeutic options of selected subtypes.

Results: The most common subtype of primary breast lymphoma is Diffuse Large B Cell Lymphoma, presenting as a breast mass, followed by various types of low grade B cell lymphomas, while lymphomas of T cell origin and Hodgkin lymphoma are exceedingly rare. Concerning breast implant-associated lymphomas, Breast Implant-Associated Anaplastic Large Cell Lymphoma is the most frequent and well-studied, presenting frequently as late seroma, whereas a variety of aggressive and low grade B cell lymphomas are described in association with breast implants. Breast parenchyma is infiltrated more commonly by systematic lymphomas of B cell origin.

Conclusions: A wide variety of haematolymphoid neoplasms can involve the breast as primary or secondary site. As clinical presentation and imaging findings are non-specific, and surgical intervention has no role in patients' treatment in most cases, it is essential to perform biopsy to every palpable breast mass to avoid malpractice in patient management.

Keywords: Breast lymphoma, BIA-ALCL, DLBCL, implants

Introduction

Breast involvement by lymphoma is considered rare and can occur either as primary site of involvement (lymphoma originating in the breast) or as secondary involvement by systematic disease disseminating to the breast [1].

Primary breast lymphoma (PBL) represents 2,2% of extranodal lymphomas and accounts for less than 0,5% of breast malignancies [2, 3]. According to Wiseman et al, diagnostic criteria for PBL have been outlined as: 1)breast tissue and lymphoma in close association 2)absence of history of lymphoma 3)absence of non-mammary organ system involvement at diagnosis. Ipsilateral lymph node involvement is in keeping with the diagnosis of PBL if breast and nodal lesions developed simultaneously [4]. As is evident from this definition, the included patients are only of Ann-Arbor's stages IE or IIE [5]. Although a minority of PBLs, special attention has been given in the recent literature at lymphoid neoplasms arising in the setting of breast implants and commonly presenting as "late seroma", due to the different pathogenetic mechanisms implicated in comparison to non implant-associated PBLs [6, 7]. Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) is the most common histological subtype in this category, but also there are several reports of B cell neoplasms that have developed in association with breast implants.

98% of the reported cases affect women but also men are rarely involved [8]. As far as non implant-associated PBLs are concerned, median age in Western countries is 62-64 years while in East Asian countries is lower (45-

53 years) [8] and the vast majority of the cases are of B cell origin, with Diffuse Large B Cell Lymphoma (DLBCL) being the most common subtype, lymphomas of T cell origin accounting for less than 6% of PBLs [1, 9] and Hodgkin lymphoma being exceedingly rare [10]. The most common presentation is a painless breast mass, much like breast carcinoma, without constitutional symptoms (present in 4% of patients), cutaneous manifestations or nipple retraction/discharge [11-16], but rarely it can mimic clinically inflammatory breast carcinoma [17]. Apart from the absence of calcifications, there are no specific imaging findings that can reliably distinguish between PBL and breast carcinoma, and the only diagnostic approach useful in differential diagnosis is biopsy [18].

Breast Implant-Associated Lymphomas BIA-ALCL

BIA-ALCL is an uncommon T cell lymphoma found to be associated exclusively with clinical history of textured implants [19-23]. In 1997, Keech et al first reported a case of anaplastic large cell lymphoma in association with silicone implants [24] and the World Health Organization [25] first included it as a provisional entity in 2016. The estimated incidence is 2,03 per 1 million person years with an estimated prevalence of 1 per 30.000 women with breast implants and 1 per 2.832 women with textured breast implants [26, 27]. The median age of diagnosis is 52 years (range 24-87) and the median time from last implant to diagnosis is 7,5 years [28].

Up to 80% of women with BIA-ALCL present with persistent seroma or periprosthetic effusion that may accompanied by breast swelling, asymmetry, or pain [29, 30]. Only 10-20% of patients present with breast mass with nodal enlargement, and cutaneous lesions, capsular contractures and B symptoms have been reported in rare cases [29, 31, 32].

The mechanisms involved in the pathogenesis of BIA-ALCL have not yet been elucidated, even though many theories have been proposed. Chronic but mild stimulation of the immune system due to the implant or bacteria around the implant are regarded to be important etiologic factors, given that textured implants are able to promote T-cell infiltration and immune response [33]. Experiments on BIA-ALCL cell lines showed links to lymphocytes with Th1/Th17 polarization in capsular tissues and surrounding seromas, suggesting that chronic bacterial antigen stimulation and sustained T-cell proliferation might support BIA-ALCL initiation and progression [34]. Moreover, other studies depicted that ALCL microenvironment is characterized by high levels of interleukin-13 and IgE, proposing possible involvement of mechanisms of chronic allergic reaction [35]. Regarding the genomic landscape of BIA-ALCL, STAT3 overactivation and presence of somatic mutations in JAK/STAT signaling pathway as well as in TP53 and DNMT3A and are considered key genomic findings [36, 37]. Furthermore, genes as chemokine receptor 6 (CCR6), MET, hepatocyte growth factor (HGF) and chemokine (C-X-C motif) ligand 14 (CXCL14), that promote cell motility processes, and peroxisome proliferator-activated receptor gamma (PPARγ) and Janus kinase 2 (JAK2) are upregulated [38].

Patients with suitable clinical context and possible signs and symptoms of BIA-ALCL should be assessed with ultrasound breast imaging or MRI [39]. Mammography has no utility in the detection of peri-capsular lymphoma. It is very important to obtain a large volume of aspiration fluid, or tissue to assess the diagnosis, and preparation of cell block is beneficiary to the patient for morphologic and immunohistochemical evaluation [40]. Morphologic features resemble systemic ALCL, whereas neoplastic cells are most commonly positive for T cell markers CD4 and CD43, apart from CD30, and are typically ALK negative [40].

Clinical presentation is directly connected to choice of treatment and prognosis [39]. Clemens et al suggested that BIA-ALCL behaves more as a solid tumor, and proposed a staging system based on the American Joint Committee on Cancer TNM system (table 1) [29]. For disease confined to the capsule total capsulectomy and removal of any mass with confirmation of negative margins is considered sufficient [41]. In absence of lymph node involvement, lymph node dissection is not usually recommended. Cases with residual disease should be managed with adjuvant radiotherapy, and in cases with lymph node involvement or distant spread systemic chemotherapy is administered, including brentuximab vedotin as a therapeutic option [42, 43]. 5-year survival of early BIA-ALCL is 89%, while adverse events are much more frequent when the tumor spreads beyond the capsule [29]. Furthermore, positive lymph nodes are reported to have significantly higher rates of death (20,8% vs 0%) and lower rates of complete remission (70,8% vs 100%) [44]. Follow-up for the next 2 years on a basis of 6 months is advised [41].

Breast-Implant Associated B cell Lymphomas

In contrast with BIA-ALCL, a broad spectrum of B cell neoplasms has been described in relation to breast implants. The question if these neoplasms are pathogenetically related to breast implants is reasonable, since chronic antigenic stimulation is described as a mechanism of B cell lymphomagenesis in the case of MALT lymphoma. Some authors postulate that systemic immune stimulation resulting from rupture, leakage or sweating of silicone implants causing B cell proliferation [45, 46]. Furthermore, what is interesting and in contrast with BIA-ALCL is that the implants implicated in the described cases are both smooth and textured [6].

Breast-implant associated B cell neoplasms include a) aggressive B cell lymphomas as plasmablastic lymphoma [47], EBV+ Large B cell Lymphoma (LBCL) [48], DLBCL [49-52] and intravascular LBCL [53], and b)low grade B cell lymphomas as marginal zone lymphoma (MZL) (describing also one case with concurrent BIA-ALCL) [54, 55], lymphoplasmacytic lymphoma (LPL) (Kraemer 2004), follicular lymphoma (FL) [56] and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with bilateral involvement [57]. A case of breast implant-associated plasmacytoma is also depicted with no evidence of systematic disease [58].

The limited number and the variation of B cell lymphoma subtypes arising in proximity to them is rendering the elucidation of their pathogenesis difficult. Yet, some authors propose that LBCLs occurring in that setting may have better prognosis in comparison with systematic DLBCL [50, 52].

PBLs of B cell origin

As mentioned above, the most frequent subtype of B cell PBL is DLBCL (56-89%), with cases also evolving from MZL [1, 9, 10, 12, 14, 59, 60], and presenting as bilateral at diagnosis or relapse in 5-25% of cases [61-68]. There are also cases related to methotrexate treatment and other immunosuppression-inducing drugs [69, 70]. Other frequent subtypes are MZL, noting also bilateral involvement (9-28%) [1, 10, 11, 60, 71-75], FL (10-19%), including a case reported in a male patient and a case with synchronous lobular carcinoma [11, 12, 74, 76, 77] and Burkitt lymphoma (<6%) [9, 78-80]. Very rare cases include CLL/SLL [11, 71], LPL [11] and mantle cell lymphoma (MCL) [81-83], and selected cases of B lymphoblastic lymphoma (B LBL) [84] and plasmablastic lymphoma occurring in an HIV+ patient [85]. In general, treatment is similar to that used for other lymphomas and depends on histological type [86]. Mastectomy offers no benefit in the treatment of PBL [9].

Primary breast DLBCL (PB-DLBCL) has been shown to have characteristic patterns of relapse distinct from those of nodal DLBCL, despite its rarity [87]. Many researchers have delineated the high propensity of PB-DLBCL to central nervous system (CNS) dissemination and CNS relapse [15, 61, 88] in 5-16% of patients. Most relapses occur <2 years following completion of therapy [13]. However, it is controversial if these facts justify CNS-directed prophylaxis [8].

The possible special genetic features of PB-DLBCL have also been investigated, in a group of patients including PB-DLBCL and composite MZL-DLBCL [89], with important findings the numeric gains of chromosomes 3 and 18 and evidence of t(14;18)(q32q21) involving IGH/MALT1. Moreover, Niitsu et al. found abnormal karyotype in 13/18 cases of PB-DLBCL in conventional cytogenetic analysis [90]. Another group identified three robust clusters based on the B-cell receptor (BCR) signaling pathway, including two recognized NF-κB-dependent and PI3K-dependent clusters and a distinct subset of PB-DLBCL with NF-κB-independent anti-apoptotic overexpression plus PI3K signaling [91].

PBLS of T cell origin

Primary PBL of T cell origin is very uncommon with selected case reports that describe cases including primary breast ALK+ ALCL, non-BIA-ALCL ALK- ALCL, peripheral T cell lymphoma not otherwise specified (PTCL NOS) and subcutaneous panniculitis-like T-cell lymphoma [10, 92-95]

Secondary involvement of breast by systematic haematolymphoid malignancies

Many different subtypes of haematolymphoid neoplasms have been reported to infiltrate breast parenchyma, more commonly of B cell type [FL (43,5%), DLBCL (34,8%), MZL (4,3%), MCL, Burkitt lymphoma, CLL, plasmablastic lymphoma) [5, 96-99]. T cell neoplasms include cases of adult T-cell leukemia-lymphoma, PTCL NOS and T LBL [93, 100]. Current literature also encompasses cases of breast involvement by of both myeloid and lymphoblastic leukemia [101].

Conclusions

A wide variety of haematolymphoid neoplasms can involve the breast as primary or secondary site, including the emerging entities of the implant-associated T and B cell lymphomas, the pathogenesis of which require further investigation. As no imaging modality confers reliable distinction between PBL and breast carcinoma, it is imperative to perform biopsy to every palpable breast mass before proceeding to surgery

REFERENCES

1. Gluskin, J., D. D'Alessio, A.C. Kim, E.A. Morris, A. Chiu, and A. Noy, Primary lymphoma of the breast: A report of two cases. Clin Imaging, 2020. 68: p. 295-299.

2. Kim, S.H., M.P. Ezekiel, and R.Y. Kim, Primary lymphoma of the breast: breast mass as an initial symptom. Am J Clin Oncol, 1999. 22(4): p. 381-3.

3. Shapiro, C.M. and D. Mansur, Bilateral primary breast lymphoma. Am J Clin Oncol, 2001. 24(1): p. 85-6.

4. Wiseman, C. and K.T. Liao, Primary lymphoma of the breast. Cancer, 1972. 29(6): p. 1705-12.

5. Picasso, R., A. Tagliafico, M. Calabrese, C. Martinoli, F. Pistoia, A. Rossi, et al., Primary and Secondary Breast Lymphoma: Focus on Epidemiology and Imaging Features. Pathol Oncol Res, 2020. 26(3): p. 1483-1488.

6. Bacon, C.M. and J.M. O'Donoghue, Commentary on: Breast Implant-Associated Bilateral B-Cell Lymphoma. Aesthet Surg J, 2020. 40(2): p. NP59-NP62.

7. Ghosh, T., E. Duncavage, N. Mehta-Shah, P.A. McGuire, M. Tenenbaum, and T.M. Myckatyn, A Cautionary Tale and Update on Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL). Aesthet Surg J, 2020.

8. Cheah, C.Y., B.A. Campbell, and J.F. Seymour, Primary breast lymphoma. Cancer Treat Rev, 2014. 40(8): p. 900-8.

9. Jennings, W.C., R.S. Baker, S.S. Murray, C.A. Howard, D.E. Parker, L.F. Peabody, et al., Primary breast lymphoma: the role of mastectomy and the importance of lymph node status. Ann Surg, 2007. 245(5): p. 784-9.

10. Talwalkar, S.S., R.N. Miranda, J.R. Valbuena, M.J. Routbort, A.W. Martin, and L.J. Medeiros, Lymphomas involving the breast: a study of 106 cases comparing localized and disseminated neoplasms. Am J Surg Pathol, 2008. 32(9): p. 1299-309.

11. Caon, J., E.S. Wai, J. Hart, C. Alexander, P.T. Truong, L.H. Sehn, et al., Treatment and outcomes of primary breast lymphoma. Clin Breast Cancer, 2012. 12(6): p. 412-9.

12. Validire, P., M. Capovilla, B. Asselain, Y. Kirova, R. Goudefroye, C. Plancher, et al., Primary breast non-Hodgkin's lymphoma: a large single center study of initial characteristics, natural history, and prognostic factors. Am J Hematol, 2009. 84(3): p. 133-9.

13. Hosein, P.J., J.C. Maragulia, M.P. Salzberg, O.W. Press, T.M. Habermann, J.M. Vose, et al., A multicentre study of primary breast diffuse large B-cell lymphoma in the rituximab era. Br J Haematol, 2014. 165(3): p. 358-63.

14. Uesato, M., Y. Miyazawa, Y. Gunji, and T. Ochiai, Primary non-Hodgkin's lymphoma of the breast: report of a case with special reference to 380 cases in the Japanese literature. Breast Cancer, 2005. 12(2): p. 154-8.

15. Yhim, H.Y., H.J. Kang, Y.H. Choi, S.J. Kim, W.S. Kim, Y.S. Chae, et al., Clinical outcomes and prognostic factors in patients with breast diffuse large B cell lymphoma; Consortium for Improving Survival of Lymphoma (CISL) study. BMC Cancer, 2010. 10: p. 321.

16. Sabate, J.M., A. Gomez, S. Torrubia, A. Camins, N. Roson, P. De Las Heras, et al., Lymphoma of the breast: clinical and radiologic features with pathologic correlation in 28 patients. Breast J, 2002. 8(5): p. 294-304.

17. Melo, A., S. Silva, C. Ferreira, R. Pereira, A. Esteves, R. Abreu Marques, et al., Primary breast lymphoma: A mimic of inflammatory breast cancer. Int J Surg Case Rep, 2018. 53: p. 410-413.

18. Harvey, J.A., M.C. Mahoney, M.S. Newell, L. Bailey, L.D. Barke, C. D'Orsi, et al., ACR appropriateness criteria palpable breast masses. J Am Coll Radiol, 2013. 10(10): p. 742-9 e1-3.

19. Leberfinger, A.N., B.J. Behar, N.C. Williams, K.L. Rakszawski, J.D. Potochny, D.R. Mackay, et al., Breast Implant-Associated Anaplastic Large Cell Lymphoma: A Systematic Review. JAMA Surg, 2017. 152(12): p. 1161-1168.

20. Kaartinen, I., K. Sunela, J. Alanko, K. Hukkinen, M.L. Karjalainen-Lindsberg, and C. Svarvar, Breast implant-associated anaplastic large cell lymphoma - From diagnosis to treatment. Eur J Surg Oncol, 2017. 43(8): p. 1385-1392.

21. Ramos-Gallardo, G., J. Cuenca-Pardo, E. Rodriguez-Olivares, R. Iribarren-Moreno, L. Contreras-Bulnes, A. Vallarta-Rodriguez, et al., Breast Implant and Anaplastic Large Cell Lymphoma Meta-Analysis. J Invest Surg, 2017. 30(1): p. 56-65.

22. O'Neill, A.C., T. Zhong, and S.O.P. Hofer, Implications of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) for Breast Cancer Reconstruction: An Update for Surgical Oncologists. Ann Surg Oncol, 2017. 24(11): p. 3174-3179.

23. Kim, B., Z.S. Predmore, S. Mattke, K. van Busum, and C.A. Gidengil, Breast Implant-associated Anaplastic Large Cell Lymphoma: Updated Results from a Structured Expert Consultation Process. Plast Reconstr Surg Glob Open, 2015. 3(1): p. e296.

24. Keech, J.A., Jr. and B.J. Creech, Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant. Plast Reconstr Surg, 1997. 100(2): p. 554-5.

25. Swerdlow, S.H., E. Campo, S.A. Pileri, N.L. Harris, H. Stein, R. Siebert, et al., The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood, 2016. 127(20): p. 2375-90.

26. Collett, D.J., H. Rakhorst, P. Lennox, M. Magnusson, R. Cooter, and A.K. Deva, Current Risk Estimate of Breast Implant-Associated Anaplastic Large Cell Lymphoma in Textured Breast Implants. Plast Reconstr Surg, 2019. 143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma): p. 30S-40S.

27. Doren, E.L., R.N. Miranda, J.C. Selber, P.B. Garvey, J. Liu, L.J. Medeiros, et al., U.S. Epidemiology of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Plast Reconstr Surg, 2017. 139(5): p. 1042-1050.

28. Co, M., T.H. Chan, K.F.S. Ip, H.M.G. Lam, G.Y. Ling, K.W.K. Ma, et al., Breast Implant-associated Anaplastic Large Cell Lymphoma - a Systematic Review with Pooled Analysis. Clin Oncol (R Coll Radiol), 2020. 32(10): p. 639-646.

29. Clemens, M.W., R.N. Miranda, and C.E. Butler, Breast Implant Informed Consent Should Include the Risk of Anaplastic Large Cell Lymphoma. Plast Reconstr Surg, 2016. 137(4): p. 1117-22.

30. Mehta-Shah, N., M.W. Clemens, and S.M. Horwitz, How I treat breast implant-associated anaplastic large cell lymphoma. Blood, 2018. 132(18): p. 1889-1898.

31. Loch-Wilkinson, A., K.J. Beath, R.J.W. Knight, W.L.F. Wessels, M. Magnusson, T. Papadopoulos, et al., Breast Implant-Associated Anaplastic Large Cell Lymphoma in Australia and New Zealand: High-Surface-Area Textured Implants Are Associated with Increased Risk. Plast Reconstr Surg, 2017. 140(4): p. 645-654.

32. McCarthy, C.M., N. Loyo-Berrios, A.A. Qureshi, E. Mullen, G. Gordillo, A.L. Pusic, et al., Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (PROFILE): Initial Report of Findings, 2012-2018. Plast Reconstr Surg, 2019. 143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma): p. 65S-73S.

33. Hu, H., A. Jacombs, K. Vickery, S.L. Merten, D.G. Pennington, and A.K. Deva, Chronic biofilm infection in breast implants is associated with an increased T-cell lymphocytic infiltrate: implications for breast implant-associated lymphoma. Plast Reconstr Surg, 2015. 135(2): p. 319-29.

34. Kadin, M.E., A. Deva, H. Xu, J. Morgan, P. Khare, R.A. MacLeod, et al., Biomarkers Provide Clues to Early Events in the Pathogenesis of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Aesthet Surg J, 2016. 36(7): p. 773-81.

35. Kadin, M.E., J. Morgan, H. Xu, A.L. Epstein, D. Sieber, B.A. Hubbard, et al., IL-13 is produced by tumor cells in breast implant-associated anaplastic large cell lymphoma: implications for pathogenesis. Hum Pathol, 2018. 78: p. 54-62.

36. Blombery, P., E. Thompson, G.L. Ryland, R. Joyce, D.J. Byrne, C. Khoo, et al., Frequent activating STAT3 mutations and novel recurrent genomic abnormalities detected in breast implant-associated anaplastic large cell lymphoma. Oncotarget, 2018. 9(90): p. 36126-36136.

37. Di Napoli, A., P. Jain, E. Duranti, E. Margolskee, W. Arancio, F. Facchetti, et al., Targeted next generation sequencing of breast implant-associated anaplastic large cell lymphoma reveals mutations in JAK/STAT signalling pathway genes, TP53 and DNMT3A. Br J Haematol, 2018. 180(5): p. 741-744.

38. Di Napoli, A., L. De Cecco, P.P. Piccaluga, M. Navari, V. Cancila, C. Cippitelli, et al., Transcriptional analysis distinguishes breast implant-associated anaplastic large cell lymphoma from other peripheral T-cell lymphomas. Mod Pathol, 2019. 32(2): p. 216-230.

39. Marra, A., G. Viale, S.A. Pileri, G. Pravettoni, G. Viale, F.

De Lorenzi, et al., Breast implant-associated anaplastic large cell lymphoma: A comprehensive review. Cancer Treat Rev, 2020. 84: p. 101963.

40. Quesada, A.E., L.J. Medeiros, M.W. Clemens, M.C. Ferrufino-Schmidt, S. Pina-Oviedo, and R.N. Miranda, Breast implant-associated anaplastic large cell lymphoma: a review. Mod Pathol, 2019. 32(2): p. 166-188.

41. de Oliveira Sermoud, L.M.C., S. Romano, M. Chveid, and G.L. da Silva Amorim, Breast Implant-Associated Anaplastic Large-Cell Lymphoma: Why Must We Learn About It? J Glob Oncol, 2019. 5: p. 1-5.

42. Clemens, M.W. and S.M. Horwitz, NCCN Consensus Guidelines for the Diagnosis and Management of Breast Implant-Associated Anaplastic Large Cell Lymphoma. Aesthet Surg J, 2017. 37(3): p. 285-289.

43. Campanale, A., R. Boldrini, and M. Marletta, 22 Cases of Breast Implant-Associated ALCL: Awareness and Outcome Tracking from the Italian Ministry of Health. Plast Reconstr Surg, 2018. 141(1): p. 11e-19e.

44. Collins, M.S., R.N. Miranda, L.J. Medeiros, M.P. Silva de Meneses, S.P. Iyer, C.E. Butler, et al., Characteristics and Treatment of Advanced Breast Implant-Associated Anaplastic Large Cell Lymphoma. Plast Reconstr Surg, 2019. 143(3S A Review of Breast Implant-Associated Anaplastic Large Cell Lymphoma): p. 41S-50S.

45. Balk, E.M., A. Earley, E.A. Avendano, and G. Raman, Long-Term Health Outcomes in Women With Silicone Gel Breast Implants: A Systematic Review. Ann Intern Med, 2016. 164(3): p. 164-75.

46. Colwell, A.S. and B. Mehrara, Editorial: US FDA Breast Implant Postapproval Studies-Long-term Outcomes in 99,993 Patients. Ann Surg, 2019. 269(1): p. 39-40.

47. Geethakumari, P.R., J. Markantonis, J.L. Shah, A. Alsuwaidan, I. Shahab, W. Chen, et al., Breast Implant-associated Plasmablastic Lymphoma: A Case Report and Discussion of the Literature. Clin Lymphoma Myeloma Leuk, 2019. 19(10): p. e568-e572.

48. Rodriguez-Pinilla, S.M., F.J.S. Garcia, O. Balague, M. Rodriguez-Justo, and M.A. Piris, Breast implant-associated Epstein-Barr virus-positive large B-cell lymphomas: a report of three cases. Haematologica, 2020. 105(8): p. e412-e414.

49. Evans, M.G., R.N. Miranda, P.A. Young, L. Pai, H.Y. Wang, S.N. Konoplev, et al., B-cell lymphomas associated with breast implants: Report of three cases and review of the literature. Ann Diagn Pathol, 2020. 46: p. 151512.

50. Larrimore, C. and A. Jaghab, A Rare Case of Breast Implant-Associated Diffuse Large B-Cell Lymphoma. Case Rep Oncol Med, 2019. 2019: p. 1801942.

51. Messer, A., H. Jenkinson, W. Wang, and M. Duvic, New B-cell Lymphomas in the Setting of a Previous Rare Breast Implant-Associated B-cell Lymphoma. Plast Reconstr Surg Glob Open, 2016. 4(11): p. e1148.

52. Smith, B.K. and S.S. Gray, Large B-cell lymphoma occurring in a breast implant capsule. Plast Reconstr Surg, 2014. 134(4): p. 670e-1e.

53. Moling, O., A. Piccin, M. Tauber, P. Marinello, M. Canova, M. Casini, et al., Intravascular large B-cell lymphoma associated with silicone breast implant, HLA-DRB1*11:01, and HLA-DQB1*03:01 manifesting as macrophage activation syndrome and with severe neurological symptoms: a case report. J Med Case Rep, 2016. 10(1): p. 254.

54. Har-Shai, L., Y. Har-Shai, I. Metanes, Y. Schindler, E. Sabo, and M. Preis, Composite breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) and extra-nodal marginal zone lymphoma (MZL) in the capsule of a silicone breast implant. Autoimmun Rev, 2019. 18(5): p. 556-557.

55. Nichter, L.S., M.A. Mueller, R.G. Burns, and J.M. Stallman, First report of nodal marginal zone B-cell lymphoma associated with breast implants. Plast Reconstr Surg, 2012. 129(3): p. 576e-578e.

56. Cook, P.D., B.M. Osborne, R.L. Connor, and J.F. Strauss, Follicular lymphoma adjacent to foreign body granulomatous inflammation and fibrosis surrounding silicone breast prosthesis. Am J Surg Pathol, 1995. 19(6): p. 712-7.

57. Bletsis, P.P., L.E. Janssen, O. Visser, S.R. Offerman, M.A. Tellier, L. Laterveer, et al., Bilateral breast implant associated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): A case report. Int J Surg Case Rep, 2020. 71: p. 341-345.

58. Beydoun, A.S., F. Ovalle, K. Brannock, and R.M. Gobble, A Case Report of a Breast Implant-Associated Plasmacytoma and Literature Review of Non-ALCL Breast Implant-Associated Neoplasms. Aesthet Surg J, 2019. 39(7): p. NP234-NP239.

59. Ryan, G., G. Martinelli, M. Kuper-Hommel, R. Tsang, G. Pruneri, K. Yuen, et al., Primary diffuse large B-cell lymphoma of the breast: prognostic factors and outcomes of a study by the International Extranodal Lymphoma Study Group. Ann Oncol, 2008. 19(2): p. 233-41.

60. Guo, H.Y., X.M. Zhao, J.N. Cao, X.C. Hu, J.L. Yin, X.N. Hong, et al., [Prognosis of primary non-Hodgkin's lymphoma of the breast]. Zhonghua Zhong Liu Za Zhi, 2008. 30(3): p. 200-2.

61. Hugh, J.C., F.I. Jackson, J. Hanson, and S. Poppema, Primary breast lymphoma. An immunohistologic study of 20 new cases. Cancer, 1990. 66(12): p. 2602-11.

62. Arber, D.A., J.F. Simpson, L.M. Weiss, and H. Rappaport, Non-Hodgkin's lymphoma involving the breast. Am J Surg Pathol, 1994. 18(3): p. 288-95.

63. Abbondanzo, S.L., J.D. Seidman, M. Lefkowitz, F.A. Tavassoli, and J. Krishnan, Primary diffuse large B-cell lymphoma of the breast. A clinicopathologic study of 31 cases. Pathol Res Pract, 1996. 192(1): p. 37-43.

64. Domchek, S.M., J.L. Hecht, M.D. Fleming, G.S. Pinkus, and G.P. Canellos, Lymphomas of the breast: primary and secondary involvement. Cancer, 2002. 94(1): p. 6-13.

65. Giardini, R., C. Piccolo, and F. Rilke, Primary non-Hodgkin's lymphomas of the female breast. Cancer, 1992. 69(3): p. 725-35.

66. Ha, C.S., P. Dubey, L.K. Goyal, M. Hess, F. Cabanillas, and J.D. Cox, Localized primary non-Hodgkin lymphoma of the breast. Am J Clin Oncol, 1998. 21(4): p. 376-80.

67. Topalovski, M., D. Crisan, and J.C. Mattson, Lymphoma of the breast. A clinicopathologic study of primary and secondary cases. Arch Pathol Lab Med, 1999. 123(12): p. 1208-18.

68. Wong, W.W., S.E. Schild, M.Y. Halyard, and P.J. Schomberg, Primary non-Hodgkin lymphoma of the breast: The Mayo Clinic Experience. J Surg Oncol, 2002. 80(1): p. 19-25; discussion 26.

69. Shen, F., G. Li, H. Jiang, S. Zhao, and F. Qi, Primary breast diffuse large B-cell lymphoma in a patient with systemic lupus erythematosus: A case report and review of the literature. Medicine (Baltimore), 2020. 99(33): p. e21736.

70. Tomita, M., S. Oura, H. Nishiguchi, and S. Makimoto, A case of bilateral methotrexate-associated diffuse large B-cell lymphomas of the breasts with unique clinical presentation and outcome. Breast Cancer, 2020. 27(5): p. 1038-1043.

71. Ganjoo, K., R. Advani, M.R. Mariappan, A. McMillan, and S. Horning, Non-Hodgkin lymphoma of the breast. Cancer, 2007. 110(1): p. 25-30.

72. Belfeki, N., S. Bellefquih, and A. Bourgarit, Breast MALT lymphoma and AL amyloidosis complicating Sjogren's syndrome. BMJ Case Rep, 2019. 12(4).

73. Ludmir, E.B., S.A. Milgrom, C.C. Pinnix, J.R. Gunther, J. Westin, L.E. Fayad, et al., Emerging Treatment Strategies for Primary Breast Extranodal Marginal Zone Lymphoma of Mucosa-associated Lymphoid Tissue. Clin Lymphoma Myeloma Leuk, 2019. 19(4): p. 244-250.

74. Martinelli, G., G. Ryan, J.F. Seymour, L. Nassi, S. Steffanoni, A. Alietti, et al., Primary follicular and marginal-zone lymphoma of the breast: clinical features, prognostic factors and outcome: a study by the International Extranodal Lymphoma Study Group. Ann Oncol, 2009. 20(12): p. 1993-9.

75. Valente, I., F. Cantergiani, A. Rinaldi, F. Russo, C. Mancini, and C. D'Aloia, Primitive marginal lymphoma of the breast. Breast J, 2020. 26(4): p. 790-791.

76. Mirkheshti, N. and M. Mohebtash, A rare case of bilateral breast lobular carcinoma coexisting with primary breast follicular lymphoma. J Community Hosp Intern Med Perspect, 2019. 9(2): p. 155-158.

77. Tiong, T.Y.V., S.M. Alsannaa, S.T.G. Soon, L.M. Poon, and Y.G. Goh, A rare case of primary follicular lymphoma of the breast in a male patient. Breast J, 2020. 26(7): p. 1404-1406.

78. Liu, Y., Giant primary breast Burkitt's lymphoma demonstrated on FDG PET/CT. Breast J, 2020. 26(5): p. 1039-1040.

79. Negahban, S., N. Ahmadi, A. Oryan, H.N. Khojasteh, A. Aledavood, H. Soleimanpour, et al., Primary bilateral Burkitt lymphoma of the lactating breast: a case report and review of the literature. Mol Diagn Ther, 2010. 14(4): p. 243-50.

80. Savvari, P., C. Matsouka, D. Barbaroussi, D. Christoulas, N. Nikitas, M.A. Dimopoulos, et al., Burkitt's lymphoma in pregnancy with bilateral breast involvement: case report with review of the literature. Onkologie, 2010. 33(8-9): p. 461-4.

81. Boullanger, N., P. Renou, J. Dugay, J. Boyer, L.R. de Yberlucea, M. Combe, et al., [Palpable mantel cell lymphoma in the breast]. Presse Med, 2001. 30(4): p. 163-5.

82. Hill, P. and M. Seale, Mantle cell lymphoma with bilateral palpable breast masses. Breast J, 2008. 14(3): p. 303-5.

83. Windrum, P., T.C. Morris, M.A. Catherwood, H.D. Alexander, D.T. McManus, and G.M. Markey, Mantle cell lymphoma presenting as a breast mass. J Clin Pathol, 2001. 54(11): p. 883-6.

84. Ishizuka, Y., Y. Horimoto, J. Fujimura, K. Ogata, F. Murakami, H. Onagi, et al., Primary breast non-Hodgkin's lymphoma in a 14-year-old girl: a case report. Surg Case Rep, 2020. 6(1): p. 87.

85. Matikas, A., G. Kanellis, C. Papadimitriou, T. Papadaki, A. Kotsakis, M.A. Dimopoulos, et al., Plasmablastic lymphoma of the breast in an immunocompetent

patient: long-lasting complete response induced by chemotherapy and autologous stem cell trasplantation. Anticancer Res, 2014. 34(9): p. 5111-5.

86. Pruthi, S., V.K. Stafyla, S.W. Phillips, L.F. Porrata, and C.A. Reynolds, Primary mammary (non-Hodgkin) lymphoma presenting as locally advanced breast cancer. Mayo Clin Proc, 2004. 79(10): p. 1310-4.

87. Aviv, A., T. Tadmor, and A. Polliack, Primary diffuse large B-cell lymphoma of the breast: looking at pathogenesis, clinical issues and therapeutic options. Ann Oncol, 2013. 24(9): p. 2236-44.

88. Hu, S., Y. Song, X. Sun, L. Su, W. Zhang, J. Jia, et al., Primary breast diffuse large B-cell lymphoma in the rituximab era: Therapeutic strategies and patterns of failure. Cancer Sci, 2018. 109(12): p. 3943-3952.

89. Kuper-Hommel, M.J., S.A. van de Schans, G. Vreugdenhil, J.H. van Krieken, and J.W. Coebergh, Undertreatment of patients with localized extranodal compared with nodal diffuse large B-cell lymphoma. Leuk Lymphoma, 2013. 54(8): p. 1698-705.

90. Niitsu, N., M. Okamoto, H. Nakamine, and M. Hirano, Clinicopathologic features and treatment outcome of primary breast diffuse large B-cell lymphoma. Leuk Res, 2008. 32(12): p. 1837-41.

91. Su, W., X. Niu, H. Ji, Y. Xu, L. Zhong, S. Wang, et al., A novel classification based on B-cell receptor signal gene expression correlates with prognosis in primary breast diffuse large B-cell lymphoma. J Cancer, 2020. 11(9): p. 2431-2441.

92. Charfi, L., Y. Houcine, Y. Yahyaoui, G. Sahraoui, N. Chraiet, K. Mrad, et al., Primary breast Anaplasic Lymphoma Kinase-positive anaplastic lymphoma in an adolescent. Breast J, 2020.

93. Gualco, G., L. Chioato, W.J. Harrington, Jr., L.M. Weiss, and C.E. Bacchi, Primary and secondary T-cell lymphomas of the breast: clinico-pathologic features of 11 cases. Appl Immunohistochem Mol Morphol, 2009. 17(4): p. 301-6.

94. Ivashkevich, Y., Y. Chernov, D. Chinenov, E. Shpot, A.A. Bessonov, A. Yoga, et al., Unusual Case of Anaplastic Large Cell Lymphoma Presenting as a Breast Mass in a Patient with no History of Breast Implants. Case Rep Pathol, 2020. 2020: p. 7543836.

95. Miranda, R.N., L. Lin, S.S. Talwalkar, J.T. Manning, and L.J. Medeiros, Anaplastic large cell lymphoma involving the breast: a clinicopathologic study of 6 cases and review of the literature. Arch Pathol Lab Med, 2009. 133(9): p. 1383-90.

96. Anagnostopoulou, V., N. Mantha, K. Sapalidis, E. Tolparidou, E. Georgiou, and T. Koletsa, Male breast involvement in chronic lymphocytic leukemia. A case report and review of the literature. Rom J Morphol Embryol, 2020. 61(1): p. 241-245.

97. Lai, C.C., S.M. Sheen-Chen, I.W. Chang, and W.K. Wang, Advanced Burkitt's lymphoma in a man presenting with a breast tumor: A case report. Breast J, 2020.

98. Wang, J., O.J. Hernandez, and F. Sen, Plasmablastic lymphoma involving breast: a case diagnosed by fine-needle aspiration and core needle biopsy. Diagn Cytopathol, 2008. 36(4): p. 257-61.

99. Zhu, D., C. Fang, H. Chen, and C. Wu, Synchronous breast carcinoma and chronic lymphocytic leukemia in a Chinese young female: a rare combination. Int J Clin Exp Pathol, 2015. 8(5): p. 5952-4.

100. Kobayashi, H., N. Asada, T. Igawa, M. Abe, Y. Meguri, D. Ennishi, et al., Adult T-cell Leukemia-lymphoma with Primary Breast Involvement: A Case Report and Literature Review. Intern Med, 2020. 59(21): p. 2757-2761.

101. Surov, A., A. Wienke, and J. Abbas, Breast leukemia: an update. Acta Radiol, 2012. 53(3): p. 261-6.

Table 1: Recommended staging system of BIA-ALCL, adapted from Mehta-Shah et al (30)

T: Tumor extent

T1 Confined to effusion or a layer on luminal side of the capsule
T2 Early capsule infiltration
T3 Cell aggregates or sheets infiltrating the capsule
T4 Infiltration beyond the capsule

N: Lymph Node Involvement

N0 No lymph node involvement
N1 One regional lymph node
N2 Multiple regional lymph nodes

M: Metastasis

M0 No distant spread
M1 Spread to other organs or distant sites

Stage

IA T1N0M0
IB T2N0M0
IC T3N0M0
IIA T4N0M0
IIB T1-3N1M0
III T4N1-2M0
IV TanyNanyM1

Is there a place for Breast Surgery in the metastatic setting?

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Breast cancer remains an important public health issue worldwide, with more than 2 million new cases diagnosed in 2018, representing about 25 per cent of all malignancies in women.

Nearly 600.000 cases were diagnosed in the European Union zone alone, with more than 137000 potential years of life lost.

The percentage of patients at any given time with metastatic recurrences is unknown, but it is estimated to range between 20-30% (1). This figure is the subject of ongoing controversy. According to SEER statistics the 18-year relative survival rate for patients diagnosed from 1990-1994 is around 71%, a number which could take us really close to this 30% figure.

Within the percentage mentioned earlier of metastatic breast cancer patients, we also included the ones presented to us with de-novo stage IV disease.

That percentage it is believed to be around 3% to 9% (2), although some consider it to be even greater.

Traditionally, loco regional treatment (surgery or radiation) has been used for these patients only for control of fungation and bleeding.

One might think that there is little space for a surgeon to talk about surgery in the metastatic setting. Indeed, this field in all surgical subspecialties has been of extreme controversy and the possibility of an intervention has not yet been fully investigated, although given the numbers and the statistics represents an important population. I shall try to express a few thoughts concerning this delicate issue.

So, what are the facts? Are there any strong data regarding this issue?

There are two trials with high level of evidence, since they are not retrospective (great majority of trials that we have in hand concerning stage IV disease in breast cancer), but randomized control ones.

The Indian TATA (open-label, randomized one center-controlled trial) (3) recruited women between 2005 and 2013, and the Turkish MF-07-01(multicenter, phase III, randomized, controlled study) (4) which selected patients between 2007 and 2012, both however with a relative low number of patients, (350 and 271 respectively). Both randomized for systemic treatment and surgery or treatment alone at diagnosis.The Indian trial was published on Lancet (Impact factor 60,392) and the Turkish trial on Annals of Surgical Oncology (Impact Factor 4,179).

It seems that there was greater homogeneity in the Indian trial, since their randomization was stratified. Tumor size unfortunately was not described in the Indian trial, while in theTurkish trial they were more T4 and triple Negative (TN) tumors in the Systemic Therapy arm.

Axillary clearance was offered in all patients in the Indian trial (even supraclavicularlinfnode debulking), while in the Turkish trial Sentinel lymph node biopsy was allowed in the node negative patients at presentation.

Radiation therapy was offered in all patients in the Indian trial while in the Turkish trial it depended on each center's protocol.

The Indian trial excluded patients with visceral crisis, multiple liver metastasis, more than 2 organs involved, bleeding or fungation that needed palliative treatment, life expectancy less than 1 year, and progression of disease or stable disease(according to WHO guidelines) in response to chemotherapy.

The Turkish exclusion criteria were a bit different and included :primary tumor not amenable for complete resection (such as tumor extending to neighboring tissues; T4a,c or inflammatory breast cancer; T4d, primary tumor with extended infection, bleeding, or necrosis, patients with poor physical condition which prevents the patient from receiving protocol driven locoregional and systemic treatment, synchronous primary cancer at the contralateral breast, previous diagnosis of other cancers (excluding basal cell skin cancer, squamous cell skin cancer, and cervical intraepithelial neoplasia), clinically involved contralateral axillary nodes, patients not suitable for adequate follow-up, and finally failure to give informed consent.

Pre-menopausal women in the Indian trial received Ovarian Function Suppression (Surgical bilateral oophorectomy and not medical), somehow in accordance with today's international guidelines (ESMO 2019) concerning treatment in pre-menopausalearly stagehigh risk of recurrence patients. Avoiding in that way the initial potential tumorflare seen with LHRH agonists', thusincreasing eligibility for the clinical trial. Unfortunately, there is no data on that in the Turkish trial.

Patient selection for these trials can be seen on figures 1 and 2.

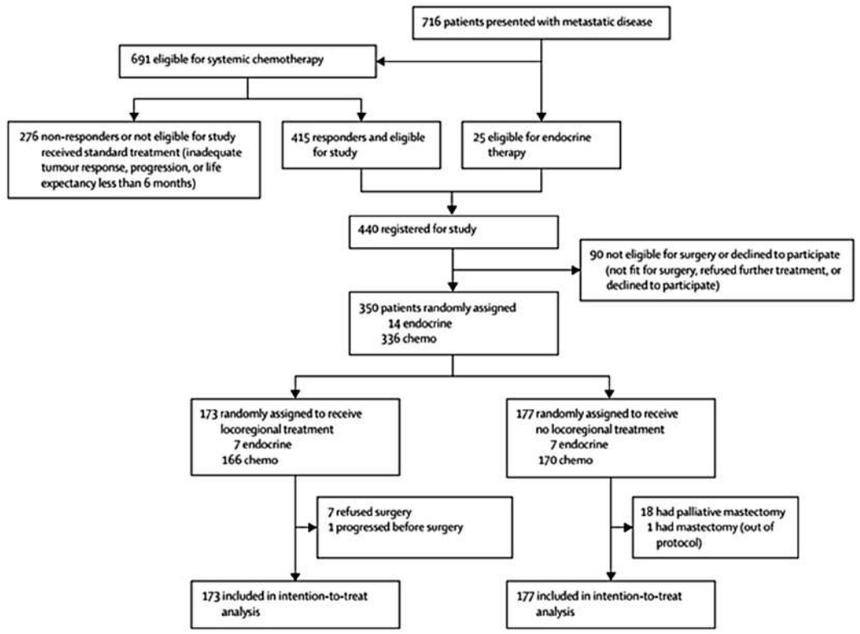

Fig. 1 Indian Tata Trial patient selection

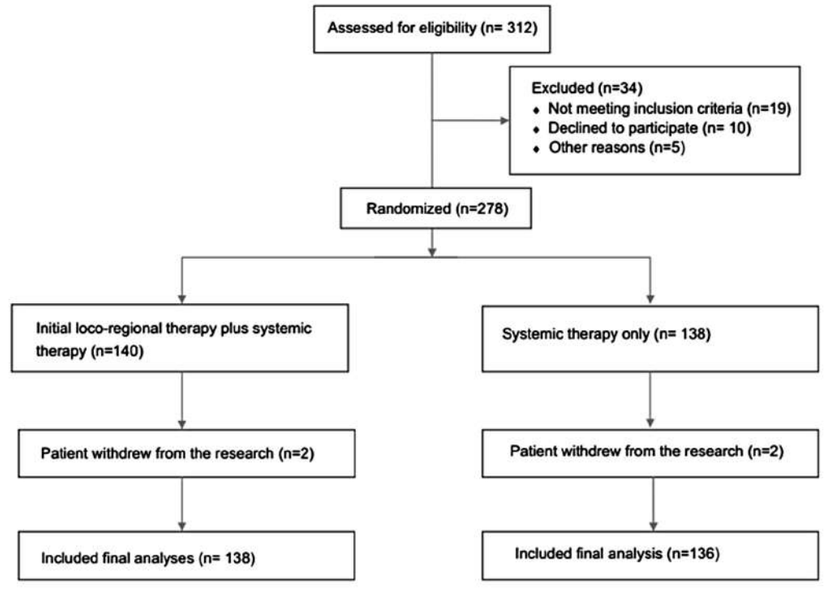

Fig. 2 Turkish trial profile MF07-01

In my mind Indian trial profile and patient selection seems more complete. Both had the same primary end point which was Overall Survival but the Turkish trial had the advantage of a much greater median follow up (60 months compared to 23 months of the Tata trial).

Finally it's worth mentioning that the Her2+ population (107/350) in the Indian trial,which represents a large portion actually, received anti-Her2 targeted therapies only if they could afford it economically. That fact by itself creates bias concerning these patients and it is obviously not matching with our today's standards of treatment and everyday practice.

Their conclusions announced were completely different.

While the Indian trial suggested that loco regional treatment did not affect Overall Survival, the Turkish trial indicated that in the 5th year of follow up in the loco regional treatment (LRT) group 41, 6% of patients were alive, in comparison to only 24, 4% in the systemic therapy arm. In this group of patients they were higher rates of ER/PR+ and lower rates of TNBC patients. Hazard of death found to be 34% lower in the LRT group with a p=0,005 which is statistically important and can be somehow trusted. More importantly Median Survival was 14 months longer in the LRT group with respect to bone only metastasis , and could be reached more than 22 months in the subpopulation with solitary bone metastasis.

Obviously more data is needed and maybe "TBCRC 0313 a prospective analysis of surgery in patients presenting with stage IV breast cancer" could provide us additional information to this issue (5). It is a multicenter prospective registry study evaluating the role of surgery for the primary tumor in de novo Stage IV disease. From 2012,127 patients from 14 sites were enrolled in 2 cohorts. All patients received 1st-line systemic therapy per treating physician.

Among responders, surgery did not impact Overall Survival irrespective of tumor subtype. These data suggest, (Level of evidence III being prospective although number of patients is again small), extreme caution in selecting patients for local therapy outside of clinical trials.

On the other hand a large population (13000 patients) based cohort retrospective study (however with a lower Level of evidence 4) has been published recently on 2020 (6) sought to reveal the distinct outcomes of stage IV breast cancer with or without

surgical intervention based on the SEER population-based data.

Their findings indicated that the surgery group was associated with a better survival compared with the non-surgery group (BCSS: HR = 0.542, 95% CI [0.499–0.589], p < 0.001; OS: HR = 0.555, 95% CI [0.512–0.601], p < 0.001).P is statistically acceptable and the CI is not wide meaning that there was enough confidence in the population characteristics chosen. Furthermore, this survival advantage persisted in all subgroups irrespective of age, race, tumor size, nodal status, histology grade, molecular subtype, chemotherapy status, radiotherapy status or status of distant metastasis.

However, for the moment and due to lack of strong evidence surgery should not be routinely recommended.

The Fifth International Consensus Conference for Advanced Breast Cancer (ABC5)took place in Lisbon, Portugal, on 14th-16th November 2019, bringing together 1500 participants from 94 countries worldwide, including health professionals, patient advocates and journalists(7).

The ABC 5 guidelines are jointly developed by ESO and ESMO, and have been endorsed by several international oncology organizations.

It was stated that removal of the primary tumor in de novo IV stage breast cancer has not been associated with prolongation of survival, with the possible exception of the subset of patients with bone only disease (LoE:1B).

Some studies suggest that surgery is only valuable if performed with the same attention to detail (e.g., complete removal of the disease R0) as in patients with early stage (LoE;2B). In general, no axillary surgery is needed, and a stable disease after systemic therapy for at least 3-6 months could also be an indication to proceed to excision of primary tumor site and possible metastasectomy.

I believe that we should focus in the subpopulation of Patients with 1 bone metastasis or oligo metastatic disease (up to 5 lesions of limited size not necessarily in the same organ).

The MF07-01 trial (Turkish trial) indicated that pre-menopausal state andsolitary bone-only metastasis lowers the risk of death in the loco-regional treatment group. A median follow up period of at least 40 months indicated significant improvement in median survival not initially detected, compared to the Indian trial.

A small but very important subset of patients with Advanced Breast Cancer, for example those with oligometastatic disease or low-volume metastatic disease that is highly sensitive to systemic therapy (or not since in the Turkish trial this subpopulation were ER/PR+,HER-), can achieve complete remission and a long survival. A multimodal approach, including loco regional treatments with curative intent (R0 Excision), could be considered for these selected patients.

What about HER2+ patients? Median Survival for them in the metastatic setting is approximately 57, 1 months. The tools we have at our disposal against HER2 enriched patients are multiple.

Recent updates concerning the Apphinity trial indicated that trastuzumab produces 40% and 34% reduction in risk of relapse and death. San Antonio updates have revealed promising news with Climb and Destiny trials. Extenet trial with Neratinib always has a special place treating ER+, HER2+ N2 high risk populations, or patients that by mistake did not receive neoadjuvant chemotherapy but went straight to the operating theatre. Its route of somministration (as well with tucatinib) is per mouth giving them high adherence and improved quality of life.

Guidelines are constantly changing. Emerging and very promising third line therapies appear improving PFS and Overall Response, finding new solutions to multi treated patients.

Especially for them systemic therapy has the upper hand and seems at the moment the only viable and most powerful option we have in our hands.

Improvements in treatment seems to gain momentum even in the HR+ population. Data from ESMO 2020 on Monarch 2 trial indicate that we can achieve significant improvement in PFS and ORR, in advanced Breast Cancer that progressed under endocrine therapy.

The use of CDK4/6 inhibitors becomes more and more prominent in our everyday practice (latest FDA approval on 2018 for Abemaciclib) even as initial therapy with AI's (MONARCH3).

All these therapies could be considered as tools that help stabilize, the patient's burden of disease. That stability can be taken into account at a later date and be used by surgeons in order to achieve longer remissions.

A final conclusion, howeveras stated earlier with insufficient evidence and a low grade of recommendation,could be that a small but important subset of patients with oligo metastatic disease (probably with one bone metastasis) stable for at least 3-6 months,could achieve long survival and remission if given the possibility, and obviously are fit, of a surgical intervention. Always taking under consideration age, performance status, comorbidities, tumor type,chemosensibilityand of course patient's preferences and possible improvement of quality of life.

Advanced/metastatic breast cancer remains a virtually incurable disease.

Unfortunately there is still a median overall survival (OS) of about 3 years and a 5-year survival rate of around 25%, even in countries without major accessibility problems.

Survival is strongly related to breast cancer subtype, and systemic treatments, not much surgical interventions. As witnessed the last years with the major advances seen in human epidermal growth factor receptor 2 (HER2)-positive populations.

Unfortunately the field of TN subtype given its enormous heterogeneity and lack of targeted therapies still remains obscure.

It is obvious that the management of Advanced Breast Cancer is complex and therefore, involvement of all appropriate specialties in a multidisciplinary team is crucial.

As stated earlier, future multicenter, larger-scale prospective studies with long-term follow-upare still warranted in order to reach good evidence allowing thus recommendations.

REFERENCES

1. Rebecca L. Siegel, Kimberly D. Miller, Ahmedin Jemal, et al. Cancer statistics 2019. CA CANCER J CLIN 2019; 69:7–34.

2. Sant M, Allemani C, Berrino F, et al, and the European Concerted Action on Survival and Care of Cancer Patients (EUROCARE) Working Group. Breast carcinoma survival in Europe and the United States. Cancer 2004; 100: 715–22.

3. Rajendra Badwe, Rohini Hawaldar, Nita Nair, Rucha Kaushik, Vani Parmar et al. Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open label randomized controlled trial. Lancet Oncol. 2015 Oct;16(13):1380-8.

4. Atilla Soran , Vahit Ozmen , Serdar Ozbas , Hasan Karanlik, Mahmut Muslumanoglu, Abdullah Igci , Zafer Canturk et al. Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01. Ann Surg Oncol. 2018 Oct;25(11):3141-3149.

5. Tari A. King, Jaclyn Lyman, Mithat Gonen, Sylvia Reyes, Eun-Sil Shelley Hwang, Hope S. Rugo, Minetta C. Liu, Judy Caroline Boughey, Lisa K. Jacobs, Kandace P. McGuire, Anna Maria Storniolo, Claudine Isaacs, Ingrid M. Meszoely, Catherine H. Van Poznak, GildyBabiera, Larry Norton, Monica Morrow, Antonio C. Wolff, Eric P. Winer, Clifford A. Hudis. A prospective analysis of surgery and survival in stage IV breast cancer (TBCRC 013). Journal of Clinical Oncology. Vol. 34, No. 15_suppl, May 20, 2016 (Volume Supplement)2016 ASCO Annual Meeting.

6. Yuxiang Lin, Kaiyan Huang, Qiang Zeng, et al. Impact of breast surgery on survival of patients with stage IV breast cancer: a SEER population-based propensity score matching analysis. March 18, 2020 PubMed 32219021

7. F. Cardoso, S. Paluch-Shimon, E. Senkus, G. Curigliano, M. S. Aapro, F. André , C. H. Barrios , J. Bergh , G. S. Bhattacharyya , L. Biganzoli, F. Boyle, M.-J. Cardoso, L. A. Carey, J. Cortés, N. S. El Saghir, M. Elzayat, A. Eniu, L. Fallowfield, P. A. Francis, K. Gelmon, J. Gligorov, R. Haidinger, N. Harbeck, X. Hu, B. Kaufman, R. Kaur, B. E. Kiely, S.-B. Kim, N. U. Lin, S. A. Mertz, S. Neciosup, B. V. Offersen, S. Ohno, O. Pagani, A. Prat, F. Penault-Llorca, H. S. Rugo, G. W. Sledge, C. Thomssen, D. A. Vorobio, T. Wiseman, B. Xu, L. Norton, A. Costa& E. P. Winer30. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5).Annals of Oncology Volume 31, Issue 12, December 2020, Pages 1623-1649.

Safe distance between patients and doctors throughout the centuries

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During the course of human history, man has always been confronted with recurrent episodes of epidemics, or pandemics. A pandemic is the global outbreak of an infectious disease. On the contrary, an epidemic is a disease which develops in a restricted area or region.

Throughout millenia, numerous episodes of epidemics/ pandemics have occurred, caused either by bacteria (b) or virus (v), such as: plague (b), smallpox (b), cholera (b), thyphus (b), leprosy (b), tubercolosis (b), measles (v), flu (v), poliomyelitis (v), ebola (v). Current pandemics are HIV/AIDS (v) and the 2019 coronavirus (v), declared a pandemic on 11 March 2020 by the World Health Organization (WHO).

In December 2019, in Wuhan, China, a new kind of respiratory disease surged due to an unknown coronavirus. Because it causes a severe acute respiratory syndrome, the International Committee on Taxonomy of Viruses named it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resultant disease as coronavirus disease 2019 (COVID-19). Dissemination was faster than expected, and cases did multiply 1879 times from January 10 to February 23 among the Chinese population. Around 81% of cases were reported as mild, 14% were reported as severe, and 5% required critical care. Mortality was calculated as 2.84% in China and 12% in European countries. A meta-analysis displayed a mortality rate of 4.3%. Besides, severe cases were commonly reported amid the elderly, patients with certain comorbidities (eg, diabetes mellitus, hypertension, and lung and/or cardiovascular diseases) and obesity.

This new illness rapidly extended worldwide and was later declared as an international public health emergency on January 30, 2020. Studies reported the human- to-human transmission by means of droplets but also by aerosols and fomites in contaminated places. The viral genome and phenotype were rapidly identified, which allowed researchers to develop specific diagnostic tests and antibody (Ab) detection assays. Due to the easy contagion and resultant brisk increased incidence, several quotidian activities have been restricted all over the world, including surgical procedures considered unessential.

Protection guidelines have been issued by WHO and other health organizations. However, when we examine patients with facial trauma or dental work has to be done, then the distance between doctor and patient is eliminated even though doctors are protected with masks or protection suits (1).
This leads to an important question: how much distance is needed between doctor and patient?

Maintaining a certain distance from others can convey a non-verbal message. According to Hall (1), an anthropologist, doctors and patients should use a wider personal distance (90 to 150 cm) for discussions with one another. This distance is also highly convenient for discussions while sitting down. This guideline applies to situations where a doctor has a discussion with a patient who is in bed.

During ward rounds, in which conversations take place at the foot of the bed, the doctor is already out of the patient's personal distance and has entered the so-called "business" distance, which is no longer suitable for confidential conversations.

In airborne infections, large droplets can travel approximately 101 cm (39.9 inches). Surgical masks provide highly effective protection against large airborne droplets. For small droplets, which can travel longer distances along unpredictable paths affected by wind gusts and other factors, traditional masks are less effective, as it is possible to inhale droplets around the sides of the masks.

When the worst outbreak of the plague was ravaging Edinburgh in 1645, Dr George Rae was appointed as the "Plague Doctor" of that city. Although the available treatments at that time were limited, he did his utmost. He lanced patients' boils to allow the poison to drain. After the wound was cleaned, he cauterized it, thereby disinfecting and sealing the wound site. To protect himself against airborne miasmas, which were then thought to be the causative agent of the plague, Dr Rae wore a special outfit. In addition to a long cloak, which protected his skin from the infectious air, he also wore a beak-like mask that was filled with spices and rose petals, which would prevent entry of the miasmas through his nose, also providing a pleasant odour. The length of the beak-like mask secured a safe distance from the patient (Fig. 2). Although miasmas do not cause the plague, as we now know, it is remarkable to note that Dr Rae's outfit still did its job by protecting him from fleabites, it enabled him to survive the plague (2).

The origin of quarantine

In 1377, Ragusa (nowadays Dubrovnik, Croatia), a city on the Dalmatian coast belonging to the Republic of Venice, during another plague's outbreak, decided to extend the isolation period from thirty days (Italian, trenta) to forty days (Italian, quaranta) thus changing the name trentina to quarantina. The term quarantine, first introduced on that occasion, is now part of the modern lexicon.

Ships and sailors, coming from plague-infested areas, had to remain in detention on surrounding islands for forty days. Visiting or disembarking were forbidden under penalty of remaining there for forty days. After the quarantine, ships were emptied, fumigated and in some cases, goods destroyed, whereas sailors undressed and were exposed to the sun.

The rationale for changing the isolation period from thirty days to forty days was not by chance, but the result of several factors: medical, alchemical and religious. Forty days was regarded as the limit of separation between acute and chronic disease. Forty days, from an alchemical point of view, corresponded to the so-called philosophical month, considered the time necessary to obtain more durable changes. Finally, forty days was the biblical flood, the period Moses remained on Mount Sinai, and Jesus in the desert.

Fig. 1 Protection suits 2020

Fig. 2 Protection suits 1645

Modern Radiotherapy in the Management of Breast Cancer

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Abstract

During the past 15 years several developments took place in the field of imaging and irradiation techniques, intensity modulated RT, hypofractionation and partial-breast irradiation. Currently, improvements in the RT technology allow us a subsequent decrease in the treatment-related complications such as fibrosis and long-term cardiac toxicity while improving the loco-regional control rates and cosmetic results. Thus, it is crucial that modern radiotherapy techniques should be carried out with maximum care and efficiency. Several randomized trials provided evidence for the feasibility of modern radiotherapy techniques in the management of breast cancer. However, the role of modern radiotherapy techniques in the management of breast cancer will continue to be defined by the mature results of randomized trials. Current review will provide an up-to-date evidence based data on the role of modern radiotherapy techniques in the management of breast cancer.

Introduction

Radiotherapy (RT) significantly reduces the risk of loco-regional recurrences after surgery by at least 70% [1]. RT has been shown to improve overall survival both for early stage breast cancer after breast-conserving surgery (BCS) and locally advanced disease after mastectomy. However, its use is usually limited by late toxicity. In patients with a long life expectancy, only modern RT techniques could obtain survival benefit that is mostly dependent on the radiation dose to the cardiac structures. During the past 15 years, several developments took place such as imaging and irradiation techniques, hypofractionation and partial-breast irradiation (PBI). Improvements in the RT technology now frequently allow us a subsequent decrease in treatment-related complications such as fibrosis and long-term cardiac toxicity while improving the loco-regional control rates and cosmetic results. Computed tomography (CT) simulators, modern-day linear accelerators, three-dimensional (3D) planning techniques and treatment verification modalities provides improved targeting and smaller irradiated volumes of normal tissue. Depending on the type of surgery and pathology reports, traditionally, conventional two-dimensional (2D) beams were used for whole-breast or chest wall irradiation. The first important challenging step in the RT technique came with the introduction of the CT-based treatment planning and 3D conformal RT (3DCRT) that provides us precise target volume definition, dose distribution calculation, and virtual simulation. Optimal shielding of organs at risk (OARs), including the heart, lungs, brachial plexus, esophagus, trachea, thyroid, and spinal cord decreased normal tissue exposure. Additionally, more homogeneous dose distribution in the clinical target volume could be obtained.

INTENSITY MODULATED RADIOTHERAPY

Intensity modulated RT (IMRT) is an advanced form of 3DCRT that became increasingly available for breast cancer. Several important studies have been carried out on the use of IMRT for breast cancer patients requiring complex breast treatments. Patients with larger breasts are more likely to have dose inhomogeneities and most likely to benefit from IMRT. It can also be the best alternative for left-sided breast cancers to decrease cardiac dose, re-irradiation, contralateral breast irradiation, PBI, and deeply seated tumor bed irradiation. The modulation of beam intensities could be determined by allowing sculpting the dose to fit a patient's anatomy. The major goal for IMRT technique is providing more homogenous dose distribution throughout the breast and concave structures such as the chest wall. This technology also allows better conformality of dose to the target and better sparing of OARs compared to non-IMRT plans. The normal tissue anatomy, the location of the primary tumor bed, and the contour of the breast should be taken into consideration when applying treatment field modifications for each individual patient. Forward planning by using the "field-in-field" technique provides excellent dose homogeneity in the irradiated areas. Thus, it is the most widely used technique in breast IMRT (Figure 1). There are also other methods, including forward-planned step and shoot breast IMRT, and an inversely planned breast IMRT technique, which can all improve dose homogeneity. IMRT planning should be performed based on 3D visualization of contours delineated on planning CT images. Proper patient positioning, immobilization, target localization, and management of breathing-related motion are essential for IMRT due to sharp dose gradient changes. Image-guided RT (IGRT) is required to precise localization of both target and normal tissues during planning and treatment procedure. The main advantage of IGRT is that it allows more accurate targeting in breast cancer by providing correct target volume delineation, obtaining simulation images, and set-up correction using images with the patient in the treatment position immediately prior to or during the treatment. A variety of imaging methods are used: gantry-mounted systems [MV electronic portal imaging device (EPID), kV/MV cone beam CT, MV systems-tomotherapy] room-mounted systems; and non-ionizing systems (ultrasound, video based systems). Besides, breath-holding techniques (using "active breathing control" devices or unassisted) and respiratory gating can effectively limit motion and decrease the dose to the heart and lungs, especially in cases in which the tumor bed is very close to the heart.

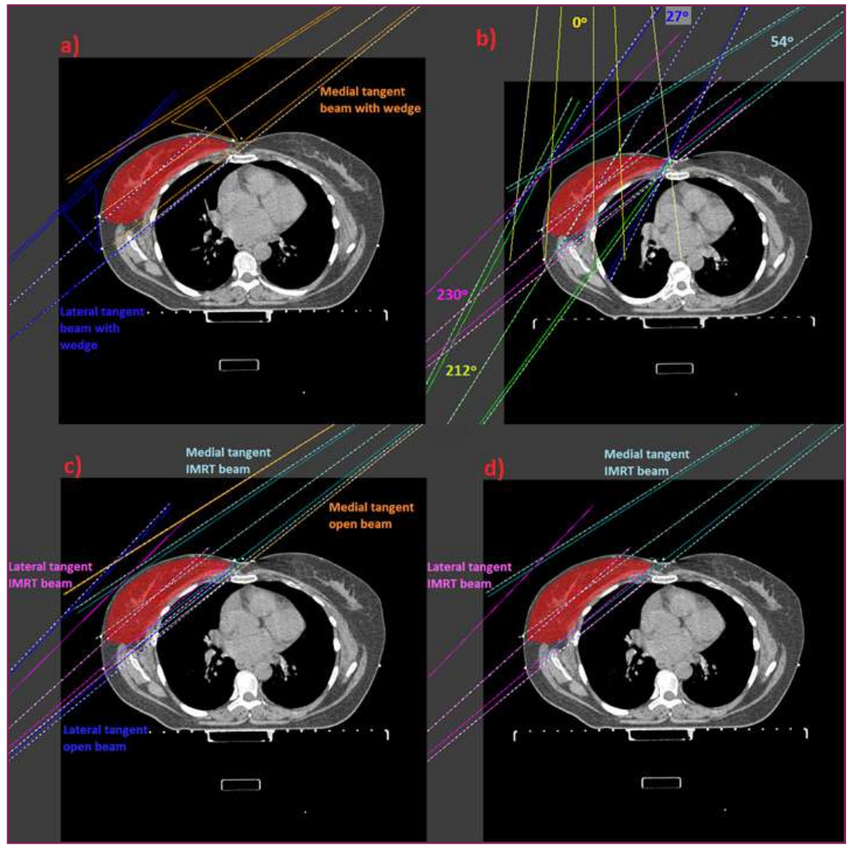

Fig. 1: Beam arrangements for a) 3D conformal tangents (3DCRT); b) multiple beam IMRT (m-IMRT); c) hybrid tangents (HT); d) IMRT tangents (t-IMRT)

TREATMENT OUTCOMES AND TOXICITY AFTER IMRT

IMRT has changed our RT practice and it is used for palliative and curative indications throughout several tumor types. The highest level of evidence by using IMRT exists particularly for breast and nasopharyngeal carcinomas. Although the clinical outcome of IMRT in breast cancers came mainly from retrospective studies, it has been assessed in three prospective randomized studies. The primary aim of these studies was to investigate treatment-induced toxicity and patients' quality of life (QOL). They showed that IMRT increased the dose homogeneity and decreased the frequency and severity of toxicity in early-stage breast cancer after BCS. However, larger sample size and longer follow-up is required to see long-term clinical outcomes and evaluate for late deleterious effects. There is only one randomized study of treatment efficacy comparing IMRT and non-IMRT[2]. Mukesh et al reported 5-year results of 815 patients randomized to either standard wedged-based tangential fields or forward planned IMRT. In this study, there was no statistically significant difference in 5-year loco-regional recurrence (2.56% and 1.35%) or overall survival (92.5% and 91.7%) rates. Additionally, there has been two reported trial designed to investigate breast cancer-related outcomes, the retrospective cohort study (n = 240) by McDonald et al [3] and the prospective cohort study (n = 332) by Morganti et al [4]. Findings did not show a statistically significant differences between IMRT and non-IMRT techniques for breast cancer related outcomes like survival, disease specific survival and freedom from contralateral breast cancer recurrence. Conventional RT causes acute skin toxicity, specifically moist desquamation in 30%-50% of patients. An inhomogeneous dose distribution and consequential hot spots of whole breast irradiation increases the rate of acute and late skin toxicity including erythema, edema, desquamation, pain, telengiectasia and fibrosis, and effects negatively cosmetic results and patient's QOL. Large breast size and dose in homogeneities > 10% as associated with a poorer clinical outcomes. In patients with larger breasts (≥ 1600 cm3 , n = 64), use of IMRT was associated with a statistically significant decrease in ≥ Grade 2 acute breast edema (0% vs. 36%, P < 0.001), and hyper pigmentation (3% vs. 41%, P = 0.001), and chronic long-term edema (3% vs. 30%, P = 0.007) compared with conventional wedge-based plans. McDonald et al reported cohort analysis on long-term outcomes of IMRT (n = 121) with conventional RT (3D RT) (n = 124). Median dose to the whole breast was 50 Gy, and median total dose to the tumor cavity was 60 Gy for both IMRT and conventional RT patient groups. IMRT resulted in reduced Grade 2 or 3 dermatitis compared with conventional RT (39% vs. 52%, P = 0.047) at median 6.3 years of follow-up. Pignol et al [5] reported the first multicenter randomized trial demonstrating a successful reduction an acute radiation skin toxicity using IMRT. Three hundred and fifty-eight patients were randomized to forward-planned IMRT or standard conventional wedge technique after complete excision of an early-stage breast cancer. IMRT significantly reduced the occurrence of moist desquamation anywhere in the breast and in the inframammary fold, with an absolute reduction of 16.6% (P = 0.002) and 17% (P = 0.001), respectively. Smaller breast size (P < 0.001) and use of IMRT (P = 0.003) strongly associated with a decreased risk of moist desquamation. Despite no statistically significant difference in the QOL or pain between the two treatment arms, there was a highly significant correlation between the development of moist desquamation and grade 2 to 3 pain score (P < 0.0001), a decrease in the global health status scale (P = 0.0019), and an increase in the breast symptoms scale (P = 0.0028). The retrospective cohort study reported by Morganti et al found that all skin-related acute toxicity reduced when standard 3D wedges were compared to simplified step and shoot IMRT technique (P < 0.05), despite with a lower total dose in the IMRT group. Only the retrospective cohort study by Freedman et al reported on the proportion of treatment time with acute dermatitis, finding a significant benefit for IMRT compared with conventional wedged based plans (18% vs. 71%, P < 0.0001). In that trial, 405 patients treated with conventional RT and 399 patients treated with IMRT. A subgroup analysis demonstrated that the time spent with radiation induced Grade 2-3 dermatitis was decreased in IMRT for all patients regardless of breast size (all P < 0.05). Barnett et al [6] reported the randomized trial demonstrating no significant differences were found in the incidence of any acute toxicity and development of any photographically assessed breast shrinkage between the IMRT or standard RT groups [odds ratio (OR), 1.51; 95% confidence interval (CI): 0.83-1.58; P = 0.41].

The decrease in acute toxicity achieved with IMRT translates into a decrease in late toxicity. There are two randomized trials showing a beneficial effect of forward planned IMRT on late toxicity. The first prospective randomized clinical trial testing the role of forward planned IMRT in terms of 5 year outcome for adverse effects was reported by Donovan et al [7] . They randomized 306 patients after BCS to standard 2D wedge-based RT or to IMRT (either IMRT with "step-and-shoot" fields or a physical 3D compensator). All were treated with a dose of 50 Gy in 25 fractions followed by a 10-Gy boost with electrons. Forward-planned IMRT significantly decreased dose in homogeneity (≥ 105% of the prescribed dose) comparing standard 2D wedge-based plans (19% vs. 92%). Results of treatment were evaluated using photographic assessment performed before RT and at 1, 2, and 5 years follow-up. The standard arm patients were 1.7 times more likely to have a change in breast appearance than the IMRT arm patients after adjustment for the year of photographic assessment (95%CI: 1.2-2.5, P = 0.008). However, there were no significant differences in outcome between randomized groups in any of the self assessed parameters, including breast pain, discomfort, hardness, body image, or QOL as measured by EORTC QLQ C30 and BR23 modules. The highest levels of dose in homogeneity in the 2D RT were seen in the upper and lower third of the breast. This suggested that dose in homogeneity in the breast increases late adverse events. The second one designed to investigate the effect of forward planned IMRT on the incidence of late radiation toxicity reported by Barnett et al [6] from Cambridge. In their study, 815 patients with early stage breast cancer were randomized to either standard wedged-based tangential fields or forward-planned IMRT. Patients were randomized if ≥ 2 cm3 receiving > 107% of prescribed dose. In this study, breast dosimetry was significantly improved with the forward-planned IMRT. All patients were treated to a dose of 40 Gy in 15 fractions. The patients in the standard RT group were more likely to develop telangiectasia than those in the IMRT group at early follow-up of only 2 years after RT completion (OR, 1.68; 95%CI: 1.13-2.40; P = 0.009). In patients who had good baseline surgical cosmesis, those randomized to IMRT were less likely to deteriorate to a moderate or poor overall cosmesis than those in the standard RT group (OR, 0.63; 95% CI: 0.39-1.03, P = 0.061). Recently, Mukesh et al [2] reported 5-year results of this study. On univariate analysis, patients receiving IMRT had superior overall cosmesis (OR, 0.68; 95%CI: 0.48 to 0.96; P = 0.027) and reduced skin telangiectasia (OR, 0.58; 95%CI: 0.36 to 0.92; P = 0.021) as compared with patients receiving standard RT arm. However, no significant difference was observed in the development of photographically assessed breast shrinkage or clinically assessed breast edema, tumor bed induration, or pigmentation. On multivariate analysis, use of IMRT was significantly associated with improved overall cosmesis (OR, 0.65; 95%CI: 0.44 to 0.98; P = 0.038) and decreased risk of skin telangiectasia (OR, 0.57; 95%CI; 0.34 to 0.95; P = 0.031). Large breast volume, poorer baseline surgical cosmesis, and tumor bed boost were also associated with suboptimal overall cosmesis on multivariate analysis.

ACCELERATED PARTIAL BREAST IRRADIATION

Multiple prospective randomized trials have demonstrated that BCS followed by whole breast RT (WBRT) as a standard treatment approach in early stage breast cancer. A large meta-analysis [1] showed that a reduction in ipsilateral breast tumor recurrence (IBTR) translated into a survival benefit of 5.4% after 15 years in early stage breast cancer patients treated with BCS. This treatment allows preservation of the breast with equivalent survival to mastectomy. In WBRT, entire breast is treated with a standard fractionation, which consists of 45-50 Gy, daily Monday to Friday over a 5- to 6-wk period. Despite being well tolerated and good cosmetic results, some patients does not receive WBRT due to long treatment duration, limited geographical access, and cost of the treatment. To address some of these issues accelerated partial breast irradiation (APBI) has gained popularity in selected patients. However, more data are needed about the use of different methods of APBI defining the optimal patient selection criteria, technique, dose and fractionation, side effects, and long-term outcomes. APBI is a reasonable alternative to WBRT in patients with BCS who have more favorable tumor characteristics. Published studies indicated that 70%-90% of IBTRs after breast conservation therapy occurred at or in close proximity to the lumpectomy cavity. Multiple phase I and several phase II trials confirmed that APBI may offer equivalent local control to WBRT with shortening conventional treatment duration from 5 to 6 wk to a single fraction or few days (1-3 wk). In APBI, only the lumpectomy cavity treated with a limited margin for potential microscopic spread. Potential advantages of APBI include shorter treatment interval, improved cosmesis due to the decreased volume of breast tissue treated, decreased heart and lung volume, and reduced cost compared with standard fractionation. Additionally, decreased volume allows acceleration and hypofractionation which might be has some theoretical radiobiological advantages. A consensus group

by American Society for Radiation Oncology (ASTRO) and the European GEC-ESTRO Cancer Working Group developed guidelines for patient selection to APBI on the basis of a variety of clinical and pathologic factors (Table 2). These guidelines categorized patients into three groups: Low-risk or suitable, intermediate-risk or cautionary group, and high risk or unsuitable group. ASTRO defined suitable group which was include patients age ≥ 60 years, without BRCA mutation, T1 (≤ 2), > 2 mm surgical margins, no lymphovascular space invasion, ER positive, unicentric, invasive ductal or other favorable histology, no extensive intraductal component, and lymph node negative optimally as part of a clinical trial. Application of APBI to intermediate or cautionary group is considered acceptable only in the context of prospective clinical trials. It is compatible with GEC-ESTRO recommendations except that tumor size (T1-2; ≤ 3 cm) and age (≥ 50 years). Modalities for APBI include brachytherapy; interstitial brachytherapy (multi-catheter interstitial implant), intracavitary brachytherapy [one balloon catheter (MammoSite ®), multiple balloon catheter (Contura®), hybrid BRT (SAVI®)], intraoperative RT (IORT); intraoperative electrons (Liac®, Mobetron®, or Novac-7®; 3-10 MeV) or low energy X-rays (Intrabeam®; 50 kV), external beam RT; 3DCRT and IMRT. Multicatheter interstitial brachytherapy, the most mature follow-up and experience of all APBI technique, is multicatheter interstitial brachytherapy (MIB) which is commonly used as a boost treatment. It is an invasive approach that multiple interstitial catheters (up to 20) are placed surrounding the tumor bed at the time of surgery or postoperatively under ultrasound guidance. The number of the catheters may vary according to the size and the shape of the target volume. After catheter placement, tumor bed plus a 1-2 cm margin is treated with LDR, HDR or PDR devices. Radioactive sources are inserted temporarily into the catheter during treatment and then removed. Most commonly used regimen is 34 Gy in 10 fractions (twice daily) over 5 d. This modality only performed at a few institutions because of the specialized training required, costly equipment, and more complex technical support needed for the procedure. It is well tolerated but dose heterogeneity within the target volume can potentially lead to fat necrosis and subcutaneous toxicity. Acute complications include pain and infection. Often oral antibiotic treatment is required and rarely requires removal of the catheters. Intracavitary brachytherapy: Intracavitary brachytherapy is the most common form of brachytherapy for APBI because of the less invasive, simple, and requires less experience. It can be applied with a single-lumen (MammoSite®) or multilumen (Contura®) balloon catheter, and elliptically shaped cluster of catheters such as SAVI®. It can be inserted into the lumpectomy cavity either at the time of surgery or postoperatively using ultrasound guidance. The balloon is then filled with saline, and an HDR radioactive source (commonly 192Ir) is inserted. After the balloon is inflated, it should be symmetric and conform to the cavity. Dose is usually prescribed to 1 cm from the balloon surface. The minimum distance between the balloon and the skin/chest wall should be ≥ 5 mm, with a shorter distance leading to a poorer cosmesis

Factor	ASTRO Suitable	GEC-ESTRO Low-risk	ASTRO Cautionary	GEC-ESTRO Intermediate-risk	ASTRO Unsuitable	GEC-ESTRO High-risk
Patient factors						
Age (yr)	≥ 60	> 50	50-59	40-50	< 50	< 40
BRCA1/2 mutation	Not present	Not defined	Not present	Not defined	Present	Not defined
Pathologic factors						
Tumor size (cm)	≤ 2	≤ 3	2.1-3.0	≤ 3	> 3	> 3
T stage	T1	T1-2	T0 or T2	T1-2	T3-4	T2 (> 3 cm), T3-4
Histology	IDC or other favorable subtypes	IDC, mucinous, tubular, medullary and colloid carcinoma	ILC allowed	ILC allowed	Any	Any
Grade	Any	Any	Any	Any	Any	Any
Pure DCIS	Not allowed	Not allowed	≤ 3 cm	Allowed	> 3 cm	Any
EIC	Not allowed	Not allowed	≤ 3 cm	Not allowed	> 3 cm	Allowed
Associated LCIS	Allowed	Allowed	Allowed	Allowed	Allowed	Allowed
Multicentricity	Unicentric	Unicentric	Unicentric	Unicentric	Multicentric	Multicentric
Multifocality	Clinically unifocal ≤ 2 cm	Unifocal	Clinically unifocal 2.1-3 cm	Multifocal (limited within 2 cm of the index lesion)	Clinically multifocal, > 3 cm	Multifocal (> 2 cm from the index lesion)
LVSI	No	Not allowed	Limited/focal	Not allowed	Extensive	Allowed
ER status	Positive	Any	Negative	Any	Any	Any
Surgical margins	≥ 2 mm	≥ 2 mm	< 2 mm	< 2 mm	Positive	Positive
Nodal factors						
N stage	pN0 (s, i+)	pN0	pN0 (s, i+)	pN1mi, pN1a	≥ pN1	pN1, ≥ pN2b
Nodal surgery	SN biopsy or ALND				None performed	
Neoadjuvant therapy	Not allowed	Not allowed	Not allowed	Not allowed	If used	If used

Table 2 American Society for Radiation Oncology and GEC-ESTRO recommendations on patient selection criteria for Accelerated Partial Breast Irradiation

Therefore, this technique may not be suitable for small breast size. The most commonly used regimen is 3.4 Gy per fraction, given twice daily, total of 34 Gy over 5 consecutive days. Potential advantage of this technique is that final pathology is known. Multi-lumen balloon catheters are more suitable for irregularly shaped lumpectomy cavities. The morbidity rates were significantly higher in patients treated with intracavitary brachytherapy with reported infection rates of 9.5% and seroma formation of 26.8% than IORT which were 1.3% and 12.9%, respectively. Fat necrosis was observed less compared to interstitial brachytherapy. External beam radiotherapy: The newest of the three major techniques with the most amounts of ongoing randomized studies is APBI with 3DCRT or IMRT. Potential advantages include noninvasiveness, knowledge of final pathology, a more homogenous dose distribution, widespread availability, less user experience, less seroma formation and infection. Additionally irregular cavities can be treated without concern for distance from the skin. The most common regimen is 38.5 Gy in 10 fractions given twice daily over 5 d. Shortcomings are the delivering more radiation to uninvolved quadrants of the breast and critical organs compared to other forms of APBI, short follow-up, uncertainty regarding the optimal dose and fractionation, and patient set-up requirement before each fraction. Intra-operative radiotherapy: The least prevalent technique is IORT using electrons (Liac®, Mobetron®, or Novac-7®; 3-10 MeV) or low energy X-rays (Intrabeam®; 50 kV). This technique is most commonly used in Europe and firstly used as a boost treatment. Most commonly applied after quadrantectomy and sentinel lymph node biopsy. A single fraction treatment can be delivered with either electrons (21 Gy in one fraction) or low energy photons (20 Gy in one fraction) immediately after surgery in the operating room. Direct visualization of the operative bed before treatment delivery reduces the likelihood of missing the target. This modality allows shielding of the skin. The potential disadvantages include increased operating times, the lack of final pathological result before delivering the RT, technical expertise and limited availability of this technique. Long-term radiobiological and cosmetic effects of such a single high fraction dose to the breast are largely unknown; however, an acceptable toxicity is achieved based on a randomized trial and a large, nonrandomized cohort study [8,9]. The risk of toxicity was low: 1.3% infections, 12.9% seroma formation, and 4.2% fat necrosis. Accelerated partial breast irradiation trials: Multiple modern phase II studies regarding APBI have reported promising local control and excellent cosmetic results. These studies showed 3%-6% of patients with 5-year local recurrence rates and 56%-99% of patients with good or excellent cosmesis. However, many Phase III studies have not been completed and primary outcome data of the largest randomized trial of WBRT vs. APBI with the longest follow-up (NSABP B-39/RTOG 0413) is not yet reported. Regarding the efficacy of APBI in a higher risk population of patients, this trial including patients with > 18 years of age, DCIS, 1-3 positive lymph nodes, and ER negative tumors will provide valuable data on literature. This trial also allows comparison of the efficacies and toxicities of three most common techniques of APBI: MammoSite®, MIB and 3DCRT. So far, only 5 randomized controlled trials have presented the final results of a completed trial . The first two published studies from the United Kingdom have important limitations including patient selection criteria and variety of techniques. At 8-year follow-up, local recurrence was increased using APBI. However, surgical margins and axillary nodal status were not evaluated and larger tumors (< 4 cm) were included in the Christie Hospital study. Similarly, in the Yorkshire Hospital trial, surgical margin status was not assessed. After the publication of these trials, there has been growing interest and published studies on APBI using more strict patient selection criteria and modern radiation technique. The first of these studies was Hungarian trial [10] compared WBRT with APBI using either HDR MIB or electrons in 258 patients with early stage breast cancer. At a median follow-up of 66 mo, the 5-year local recurrence rate was 4.7% for APBI and 3.4% for WBRT arm (P = 0.50). Excellent to good cosmesis was noted in 77.6% and 62.9%, respectively (P = 0.009). There were no significant differences in disease-free or overall survival. Since another study opened with the same patients group covering GEC-ESTRO trial, this study was stopped early. The second completed randomized trial, the TARGIT-A trial (n = 2232), compared WBRT with single dose IORT with or without boost after BCS [11]. With a median follow-up of 2 years, the estimated 4-year local recurrence rate was 1.2% for IORT group and 0.95% for WBRT group (P = 0.41). The incidence of major toxicities were 3.9% and 3.3%, respectively (P = 0.44). Fourteen percent of patients received WBRT in addition to IORT according to the final pathology report.

Five-year results of this trial recently published. Supplemental WBRT after IORT was applied in 15.2% of patients who received IORT in the prepathology stratum. The 5-year risk for local recurrence in the conserved breast was 3.3% for IORT vs. 1.3% for WBRT (P = 0.042). Overall, breast cancer mortality was similar between two groups (2.6% vs. 1.9%, P = 0.56) but there were significantly fewer non-breast cancer deaths with IORT (1.4% vs. 3.5%, P = 0.0086). Grade 3-4 skin complications were significantly reduced with IORT (P = 0.029). The last randomized trial was reported by Veronesi et al in 2013 [12]. They randomized 1305 patients after BCS to WBRT or IORT with electrons (21 Gy). After a median follow-up of 5.8 years, 35 patients in the IORT group and four patients in the WBRT group had had an IBTR (P < 0.0001). Five-year overall survival did not differ between the groups (96.8% in the IORT vs. 96.9% in the WBRT, P = 0.59). Skin complications were significantly reduced with IORT (P = 0.0002). However, longer follow-up is required before routinely adopting these modern radiation techniques into clinical practice. With regard to cosmesis, the analysis of all major studies shows conflicting data about the outcomes with APBI. Vicini et al [13] reported the long-term experience of APBI with Mammosite (1440 patients were treated). With a median follow-up of 4.5 years, 5-year local recurrence rate was 3.8% and 91% of patients had a good or excellent cosmetic result. The prospective study by Jagsi et al reported an early closure of an APBI study with IMRT. They showed unacceptable cosmesis in 7 of 34 patients with a median follow-up of 2.5 years. Toxicity of 3DCRT APBI was reported by Hepel et al in accordance with the technique and dose-volume constraints of the NSABP/RTOG 0413 protocol. At 15 mo, grade 2-4 late toxicity was observed in 10% of patients. The preliminary results of the RAPID study was presented at American Society for Radiation Oncology (ASTRO) 2012 and showed that the toxicity with 3DCRT APBI (32%) was more severe than WBRT (19%) at 3 years. In another prospective study (n = 50), 54% of incidence of moderate to severe fibrosis and 35% of fat necrosis was seen with long-term follow-up after the use of interstitial brachytherapy. The total dose was significantly correlated with the poor cosmetic results. Livi et al [14] detected significant improvements in acute grade 1-2 skin toxicity, favoring APBI with IMRT over convention ally fractionated WBRT. The preliminary results of the NSABP B-39/RTOG 0413 trial also have been reported equivalence of cosmesis to WBRT. Veronesi et al reported on 1822 patients treated with IORT (electron, 21 Gy) after quadrantectomy. With a mean follow-up of 36.1 mo, the local recurrence rate and the recurrence rate outside the treatment area were 2.3% and 1.4%, respectively. Recently, ELIOT study was evaluated regarding GEC-ESTRO recommendations and local recurrence rates were reported. They found that 5-year local recurrence was 1.9% for good candidates, 7.4% for possible candidates, and 7.7% for contraindication groups. It is clearly shows for this technique that accurate patient selection is so important. In order to reach a conclusion that APBI is an acceptable alternative to WBRT, further studies with longer follow-up are needed. Until this date; when treating patients with APBI, consensus guidelines should be considered.

HYPOFRACTIONATED WHOLE BREAST RADIOTHERAPY

Hypofractionated RT involves fewer treatments, delivers a higher dose per treatment, and shorter overall treatment time (approximately 5 wk) compared to conventional RT. The role of hypofractionated WBRT after BCS has been clearly defined by four prospective randomized trials (Table 4). The Royal Marsden Hospital and Sutton and Gloucestershire Oncology Centre trial [15,16] randomizing patients in the same 5-wk length of treatment between conventional RT (50 Gy in 25 fractions) and hypofractionated WBRT (39 Gy or 42.9 Gy in 13 fractions). There was a significant reduction in the rate of local recurrence using hypofractionated WBRT (12.1% for 50 Gy, 14.8% for 39 Gy, and 9.6% for 42.9 Gy; P = 0.027). However, there was a statistically significant change in breast appearance with the largest daily fraction size to 42.9 Gy compared with 39 Gy and 50 Gy. START trials (A and B) [17, 18] reported the experience of WBRT and hypofractionation. Trial A compared 50 Gy in 25 fractions, 41.6 Gy in 13 fractions, or 39 Gy in 13 fractions within same 5 wk length of treatment. Trial B compared 50 Gy in 25 fractions over 5 wk vs. 40 Gy in 15 fractions over 3 wk. The 5-year local control, disease free survival, and overall survival with the hypofractionation arms similar to conventional RT arm. Ten-year results of these studies have been published recently and similar breast cancer related outcomes have been reported. In trial A, moderate or marked breast induration, telangiectasia, and breast edema were significantly less common in the 39 Gy group than in the 50 Gy group. Normal tissue effects did not differ significantly between 41.6 Gy and 50 Gy groups. In trial B, breast shrinkage, telangiectasia, and breast edema were significantly less common in the 40 Gy group than in the 50 Gy group. Whelan et al) [19] randomized 1234 patients to either 42.5 Gy in 16 fractions over 22 d vs. 50 Gy in 25 fractions over 35 d. At 10 years, a non-significant trend was seen for a lower local recurrence in the hypofractionated arm than in the conventional RT arm (6.2% and 6.7%, respectively). There were no differences in the survival, breast cancer mortality, and cosmetic outcomes. Additionally, ongoing UK FAST trial [20] comparing 50 Gy in 25 fractions vs. 28.5 or 30 Gy in 5 once-weekly fractions of 5.7 or 6 Gy, respectively. Preliminary results of this study showed inferior outcome for the ultra short fractionation regimen. In a meta-analysis of the START A and B trials and pilot study from the Ontario Clinical Oncology Group found no significant difference between the hypofractionated WBRT and conventional RT for grade 3 tumors.

Cochrane review comparing the major trials of hypofractionated WBRT with conventional RT have shown that there is no difference in local recurrence rate (RR, 0.97; P = 0.78), breast appearance (RR, 1.17; P = 0.09), or 5-year survival (RR, 0.89; P = 0.16)[98]. However, acute skin toxicity was significantly lower with conventional RT (RR, 0.21; P = 0.007). Despite the successful outcomes of hypofractionated WBRT, there are many unanswered questions regarding this issue. Firstly, all of these randomized studies did not have routine boost irradiation which was standard after WBRT for invasive breast cancer. Therefore, the optimal boost method after hypofractionated WBRT is still unknown. However, three phase I-II studies have reported favorable early local control and cosmesis of hypofractionated WBRT with a concurrent boost for early stage breast cancer. Grade 3 or higher skin toxicity was not reported in these trials. Secondly, patients who underwent hypofractionated WBRT are often low risk patients, and have small breast size and small chest wall separation. Especially, application of this technique to high risk patients whom required chemotherapy remains investigational until mature data from IMPORT and RTOG 1005 can provide efficacy and safety of hypofractionated WBRT in this group. Finally, Coles et al suggested that hypofractionated WBRT should be applied to only right-sided breast cancer to reduce the RT doses per fraction received by the heart and coronary arteries. Nowadays, the ASTRO has published guidelines for the implementation of hypofractionated WBRT in early stage breast cancer. Hypofractionated WBRT can be an acceptable treatment option outside of a clinical trial including patients with pT1-2 tumors, No nodal disease, age > 50 years old, patients who do not receive chemotherapy, and patients who do not require tumor bed boost.

CONCLUSION

Phase III randomized trials demonstrated superiority of IMRT over conventional techniques in terms of both acute and late complications after breast conserving surgeries. Dosimetric trials showed that IMRT also improves breast and regional lymphatic coverage while decreasing radiation doses to heart, lungs, and contralateral breast tissues compared to old-fashioned radiotherapy techniques. Hypofractionated regimens such as APBI may improve therapeutic index after breast conserving surgery. Furthermore, the duration of therapy will be shorter, and the workload in radiotherapy department will be minimized by those hypofractionated regimens. However, current standard of care after breast conserving surgery is still whole breast irradiation, not APBI. The role of hypofractionated regimens will be defined by mature results of both completed and ongoing randomized trials in the next decade. Finally, it is noteworthy that quality assurance is crucial for the application of those challenging radiotherapy techniques. Even minor errors may result in catastrophic outcomes. Therefore, planning and implementing of modern radiotherapy techniques in breast cancer should be carried out with maximal care. ■

REFERENCES

1. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans E, Godwin J, Gray R, Hicks C, James S, MacKinnon E, McGale P, McHugh T, Peto R, Taylor C, Wang Y. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. Lancet 2005; 366: 2087-2106

2. Mukesh MB, Barnett GC, Wilkinson JS, Moody AM, Wilson C, Dorling L, Chan Wah Hak C, Qian W, Twyman N, Burnet NG, Wishart GC, Coles CE. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. J Clin Oncol 2013; 31: 4488-4495

3. McDonald MW, Godette KD, Butker EK, Davis LW, Johnstone PA. Long-term outcomes of IMRT for breast cancer: a single-institution cohort analysis. Int J Radiat Oncol Biol Phys 2008; 72: 1031-1040

4. Morganti AG, Cilla S, Valentini V, Digesu' C, Macchia G, Deodato F, Ferrandina G, Cece MG, Cirocco M, Garganese G, Di Lullo L, Traficante D, Scarabeo F, Panunzi S, De Gaetano A, Sallustio G, Cellini N, Sofo L, Piermattei A, Scambia G. Phase I-II studies on accelerated IMRT in breast carcinoma: technical comparison and acute toxicity in 332 patients. Radiother Oncol 2009; 90: 86-92

5. Pignol JP, Olivotto I, Rakovitch E, Gardner S, Sixel K, Beckham W, Vu TT, Truong P, Ackerman I, Paszat L. A multicenter randomized trial of breast intensity-modulated radiation therapy to reduce acute radiation dermatitis. J Clin Oncol 2008; 26: 2085-2092

6. Barnett GC, Wilkinson JS, Moody AM, Wilson CB, Twyman N, Wishart GC, Burnet NG, Coles CE. Randomized controlled trial of forward-planned intensity modulated radiotherapy for early breast cancer: interim results at 2 years. Int J Radiat Oncol Biol Phys 2012; 82: 715-723

7. Donovan E, Bleakley N, Denholm E, Evans P, Gothard L, Hanson J, Peckitt C, Reise S, Ross G, Sharp G, SymondsTayler R, Tait D, Yarnold J. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol 2007; 82: 254-264

8. Veronesi U, Orecchia R, Luini A, Galimberti V, Zurrida S, Intra M, Veronesi P, Arnone P, Leonardi MC, Ciocca M, Lazzari R, Caldarella P, Rotmensz N, Sangalli C, Sances D, Maisonneuve P. Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. Breast Cancer Res Treat 2010; 124: 141-151

9. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, Alvarado M, Flyger HL, Massarut S, Eiermann W, Keshtgar M, Dewar J, Kraus-Tiefenbacher U, Sütterlin M, Esserman L, Holtveg HM, Roncadin M, Pigorsch S, Metaxas M, Falzon M, Matthews A, Corica T, Williams NR, Baum M. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet 2010; 376: 91-102

10. Polgár C, Fodor J, Major T, Németh G, Lövey K, Orosz Z, Sulyok Z, Takácsi-Nagy Z, Kásler M. Breast-conserving treatment with partial or whole breast irradiation for lowrisk invasive breast carcinoma--5-year results of a randomized trial. Int J Radiat Oncol Biol Phys 2007; 69: 694-702

11. Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, Alvarado M, Flyger HL, Massarut S, Eiermann W, Keshtgar M, Dewar J, Kraus-Tiefenbacher U, Sütterlin M, Esserman L, Holtveg HM, Roncadin M, Pigorsch S, Metaxas M, Falzon M, Matthews A, Corica T, Williams NR, Baum M. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet 2010; 376: 91-102

12. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, Luini A, Veronesi P, Galimberti V, Zurrida S, Leonardi MC, Lazzari R, Cattani F, Gentilini O, Intra M, Caldarella P, Ballardini B. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet WJCO|www.wjgnet.com 437 August 10, 2014|Volume 5|Issue 3| Ozyigit G et al. Modern radiotherapy techniques in breast cancer Oncol 2013; 14: 1269-1277

13. Vicini F, Beitsch P, Quiet C, Gittleman M, Zannis V, Fine R, Whitworth P, Kuerer H, Haffty B, Keisch M, Lyden M. Five-year analysis of treatment efficacy and cosmesis by the American Society of Breast Surgeons MammoSite Breast Brachytherapy Registry Trial in patients treated with accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys 2011; 79: 808-817

14. Livi L, Buonamici FB, Simontacchi G, Scotti V, Fambrini M, Compagnucci A, Paiar F, Scoccianti S, Pallotta S, Detti B, Agresti B, Talamonti C, Mangoni M, Bianchi S, Cataliotti L, Marrazzo L, Bucciolini M, Biti G. Accelerated partial breast irradiation with IMRT: new technical approach and interim analysis of acute toxicity in a phase III randomized clinical trial. Int J Radiat Oncol Biol Phys 2010; 77: 509-515

15. Yarnold J, Ashton A, Bliss J, Homewood J, Harper C, Hanson J, Haviland J, Bentzen S, Owen R. Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial. Radiother Oncol 2005; 75: 9-17

166. Owen JR, Ashton A, Bliss JM, Homewood J, Harper C, Hanson J, Haviland J, Bentzen SM, Yarnold JR. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol 2006; 7: 467-471

17. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, BarrettLee PJ, Bliss JM, Brown J, Dewar JA, Dobbs HJ, Haviland JS, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Morgan DA, Owen JR, Simmons S, Sumo G, Sydenham MA, Venables K, Yarnold JR. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008; 9: 331-341

18. Bentzen SM, Agrawal RK, Aird EG, Barrett JM, BarrettLee PJ, Bentzen SM, Bliss JM, Brown J, Dewar JA, Dobbs HJ, Haviland JS, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Morgan DA, Owen JR, Simmons S, Sumo G, Sydenham MA, Venables K, Yarnold JR. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008; 371: 1098-1107

19. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, Shelley W, Grimard L, Bowen J, Lukka H, Perera F, Fyles A, Schneider K, Gulavita S, Freeman C. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010; 362: 513-520

20. Agrawal RK, Alhasso A, Barrett-Lee PJ, Bliss JM, Bliss P, Bloomfield D, Bowen J, Brunt AM, Donovan E, Emson M, Goodman A, Harnett A, Haviland JS, Kaggwa R, Morden JP, Robinson A, Simmons S, Stewart A, Sydenham MA, Syndikus I, Tremlett J, Tsang Y, Wheatley D, Venables K, Yarnold JR. First results of the randomised UK FAST Trial of radiotherapy hypofractionation for treatment of early breast cancer (CRUKE/04/015). Radiother Oncol 2011; 100: 93-100

Dear Colleagues,

Dear Friends,

It is with great pleasure that, we are inviting you to the 21st SIS World Congress on Breast Cancer and Breast Healthcare, which will take place, in one of the most cosmopolitan Greek islands, the island of Rhodes, at Rodos Palace, Luxury Convention Resort on 21-24 September 2022. We were forced to postpone it to September 2022 due to the corona virus pandemic issue.

This Congress may bring back some memories to the older Colleagues from the unforgettable 7th International Congress of the SIS of 1992, in the island of Rhodes, the island of Knights, as it is widespread and famous, is waiting to treat us with the unique Greek insular hospitality, in its special blend of medieval and traditional character, that is encircled harmonically with a pure nature.

The core framework of the Congress will be the Scientific Program, which has been developed by a dedicated Scientific Committee.

The 21st SIS World Congress on Breast Cancer and Breast Health Care in Rhodes will help all attending delegates and participants to advance their knowledge and navigate the complex world of today's most effective initiatives and best practices across the full spectrum of Breast Cancer and Breast Healthcare and additionally for us to meet each other and make new friends from all around the world.

A daily cruise to the Island of Kos, the birth place of Hippocrates, in order to watch the representation of the Oath of Hippocrates will take place the Sunday the day after the end of the Congress .

Join us for the 21st SIS World Congress on Breast Cancer and Breast Health Care and experience the Greek hospitality.

Best wishes,

Pr Lydia Ioannidou-Mouzaka MD, PhD
President of the Congress
Surgeon-Gynecologist-Senologist
p. President of the Senological International Society (SIS)

Dr Paris Kosmidis MD, PhD
President of the Scientific Committee
Medical Oncologist
p. President of ESMO

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IN COLLABORATION WITH

SENOLOGIC HELLENIC SOCIETY

21st

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SEPTEMBER 21-24, 2022 | RHODES ISLAND - GREECE

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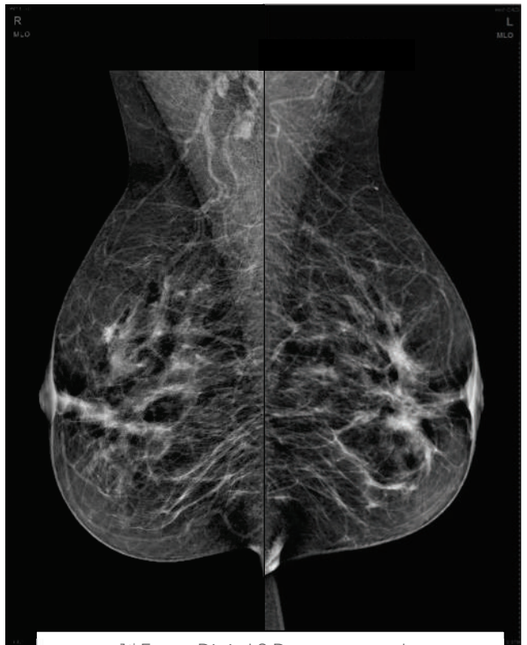
Streamlining diagnostic imaging with ProFound AI™ for Tomosynthesis

A 58-year-old asymptomatic woman presented in the diagnostic mammography department for digital mammography. She did not want to participate in the organized mammography screening program.

1st Exam: 2D digital mammography

The radiologist performed a palpation exam that was normal, however, on the mammogram, the radiologist identified an architectural distortion combined with calcifications in the left retro areolar tissue. Also, a group of calcifications was identified in the right breast. No priors were available.



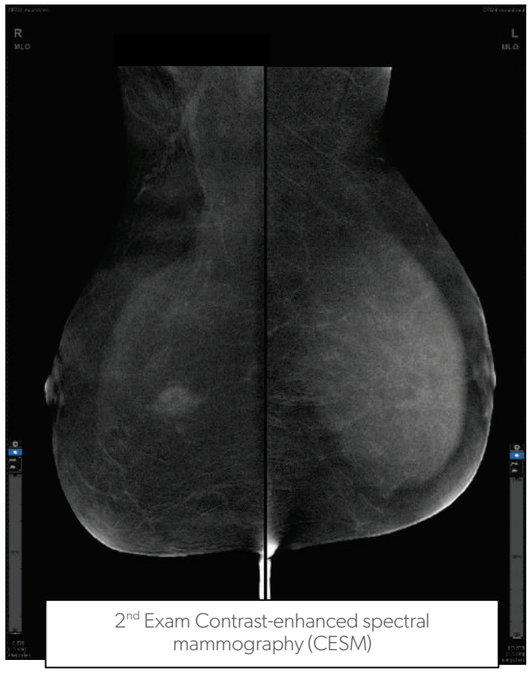
1st Exam: Digital 2 D mammography

The lesion in the left breast was assessed as BI-RADS 4 (suspicious), and the calcifications in the right breast were assessed as BI-RADS 2 (benign).

An unblinded double reading was performed and the second reader agreed with the first reader. An ultrasound-guided biopsy of the lesion in the left breast was recommended, and the patient was referred to a third radiologist.

2nd Exam: Contrast-enhanced spectral mammography

The third radiologist was not sure if the lesion identified on ultrasound in the left breast correlated to the mammographic findings, so a contrast-enhanced spectral mammography (CESM) was performed. The policy of the institute is to perform CESM bilaterally, which revealed a contrast-enhancing lesion in the right breast, but no findings in the left breast.



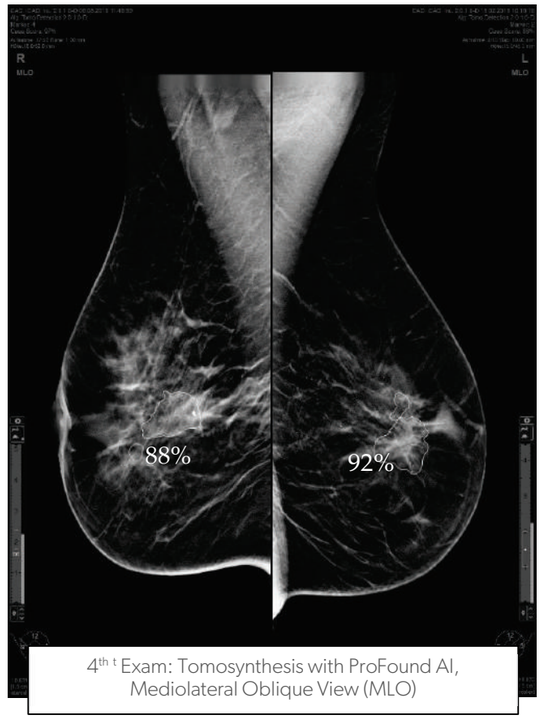
2nd Exam Contrast-enhanced spectral mammography (CESM)

3rd Exam: Ultrasound guided biopsy:

An ultrasound of the right breast was then performed, which revealed an ill-defined hypoechoic area with dilated ducts and calcifications. An ultrasound-guided biopsy with clip placement revealed this lesion to be a ductal carcinoma in-situ (DCIS).

4th Exam: Tomosynthesis with ProFound AI

Bilateral 2-view digital breast tomosynthesis with ProFound AI was then obtained, which detected calcifications adjacent to the clip in the right breast with a high lesion score. In the left breast, ProFound AI detected an architectural distortion and calcifications with high lesion scores. Stereotactic biopsy of the lesion in the left breast showed it to be a radial scar.



4th t Exam: Tomosynthesis with ProFound AI, Mediolateral Oblique View (MLO)

Conclusions/Hypothesis:

If the initial mammography would have been performed with digital breast tomosynthesis and ProFound AI, the right and left breast lesions could have been detected and diagnosed without adding CESM to the diagnostic pathway, avoiding additional radiation, time and cost. The use of ProFound AI could have led to biopsy recommendations for both the right and left breast lesions right away, rather than only the left breast lesion, which turned out to be less significant histopathologically. Again, saving time and advancing the time to appropriate care for the patient.

As a physician's reading can often be subjective, and radiologists are often distracted and/or influenced by their professional experience, it is possible to underestimate masses or calcifications and give low BI-RADS categories, such as in this case with the right breast. In order to have additional objective information, it is recommended to use ProFound AI with screening digital breast tomosynthesis in order to reduce false negative readings and to detect cancers earlier and more efficiently. Further studies using ProFound AI with screening programs are needed to support this hypothesis.

-- Dr. Axel Gräwingholt, Head of the Department of Mammography Screening, Radiologie am Theater, Paderborn, Germany

About iCAD, Inc.

Headquartered in Nashua, NH, iCAD is a global leader in medical technology providing innovative cancer detection and therapy solutions. For more information, visit www.icadmed.com.

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4 - 5 / 6 / 21

16-17 / 7 / 21

24-25 / 9 / 21

22-23 / 10 / 21

19-20 / 11 / 21

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More information in the next Issue

AI WILL CHANGE THE WAY PATIENTS ARE DIAGNOSED

As advanced diagnostic systems collect high-volume data too vast to evaluate efficiently, AI is learning to close the gap.

Jacques Souquet, Ph.D.
Founder. Chief Strategic and Innovation Officer at SuperSonic Imagine

The market for artificial intelligence (AI) medical imaging is stated to reach $2 billion by 2023.[1] Adoption is expected to nearly triple, as 30 percent of facilities plan to add AI, in addition to the 17 percent that already utilize it.[2]

Why the dramatic boost in popularity? Because this technology is so badly needed. Current imaging modalities collect vast volumes of data in just a few minutes. Physicians are accustomed to viewing the data through graphic reports, with color-coded images. Suspicious results or indicators of specific pathologies are compared against normative databases. Still, physicians spend time reviewing different reports on different testing modalities and judging how the pieces fit together for their patients. All the while, the number of modalities and the volume of data they collect continue to grow.

AI is changing this process. Already, AI systems are evaluating images and data from multiple modalities and drawing conclusions that ultimately inform physicians' decisions. In the future, as the high-volume flow of data continues to strengthen, it will become routine for physicians to rely on AI for fast, accurate diagnosis.

More help with more data

According to a recent study, to meet workflow demands in an 8-hour work day, a radiologist has to assess a diagnostic image every 3 to 4 seconds.[3] That isn't feasible, so the current volume of images and data is now simply too large to interpret without help.

Enter AI. AI can integrate machines' cognitive functions, including data and trend compilation and building models, to make diagnoses more accurate. For example, when a lung CT scan acquires 5,000 images in about 3 minutes, AI can test the images for relevance and indicate the most important ones for physicians to review, as well as what diagnostic probabilities for those images. As machines are used on more patients, acquiring more data, they actually learn independently and continually optimize these functions.

Advancing medicine's "three P's"

AI is poised to advance the all-important three P's: predictive, preventive, and personalized medicine. For example, AI-enabled ultrasound can predict the severity of liver disease, such as nonalcoholic steatohepatitis (NASH). It can prevent advanced disease by screening for early indicators. Certainly, AI excels at personalizing medicine by understanding the differences in each patient's disease, enabling physicians to tailor treatment to each person.

continued...

INSTRUCTIONS TO AUTHORS

"MASTOLOGIA" is the official scientific journal of the Hellenic Senologic Society (HSS). Its main objective is to publish original articles, reviews and case reports on breast diseases. The journal "Mastologia" is also concerned in the continuous education of the Senologists and aims at promoting the science of Senology. The journal publishes papers, which concern clinical research and scientific achievements. It also welcomes clinical investigations, basic applied laboratory research as well as new data and recent developments of senological interest. Papers published in other Journals are not accepted.

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In case of reports, the authors should not exceed four (4). In review articles the authors should not exceed the number of two (2). The following should be observed in the case of clinical studies:

a) The authors should state that the research was conducted according to the principles as have set forth by the Helsinki Declaration of 1975.

b) In the Studies that involve human subjects, a statement-approval from the appropriate human ethics committees should be obtained.

c) A statement-approval of the competent scientific committee of the centre in which the research work was carried out, pertaining to the protocol of the perspective studies, should be included.

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The revised manuscript with an accompanying letter signed by the corresponding author, in which he declares that all corrections have been done. The final decision for acceptance of the manuscript lies on the Editorial Board that decides for approval, or return of manuscript for supplementary information, decision for re-approval or to reject the manuscript. As soon as the paper is accepted and has been allotted final publication, a proof is dispatched to the authors for final checking.

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Original Articles: maximum 3,000 words, 30 references, 6 tables and 10 figures, Abstract 200 words in English and 300 words in Greek
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Article structure

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1. Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. J Sci Commun 2000;163:51–9.
Reference to a book:
2. Strunk Jr W, White EB. The elements of style. 3rd ed. New York: Macmillan; 1979.
Reference to a chapter in an edited book:
3. Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York:
E-Publishing
Inc; 1999, p. 281–304.

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