Ministry of Health
General Directorate of Medical Devices and Pharmaceuticals Services
Unit 5 - MD Vigilance System and Inspections -

OUTCOMES AND KNOWLEDGE GAINED FROM VIGILANCE AND SURVEILLANCE ACTIVITIES ON BIA-ALCL ISSUE CARRIED OUT BY THE COMPETENT AUTHORITY: A 7-YEAR REPORT

A. Campanale, L. Lispi, A. Iachino

BIA-ALCL MANAGEMENT

First cases at the end of 2014

A tal fine, si chiede che tutti i pazienti portatrici di protesi mammarie ed affetti da un *sieroma periprotesico tardivo "freddo"* (comparso a distanza di almeno 6 mesi dall'intervento, non su base traumatica o infettiva), specie se *persistente e recidivante*, debbano essere sottoposti ad un agoaspirato sotto controllo ecografico di almeno 20 cc di siero e questo inviato all'esame citologico. Il campione, centrifugato e strisciato sul vetrino, dovrà essere sottoposto a colorazione Giemsa e Papanicolaou e in caso di positività certa o dubbia per anomalie cellulari i pazienti dovranno essere inviati ad un centro specializzato di emopatologia per la conferma citologica di ALCL.

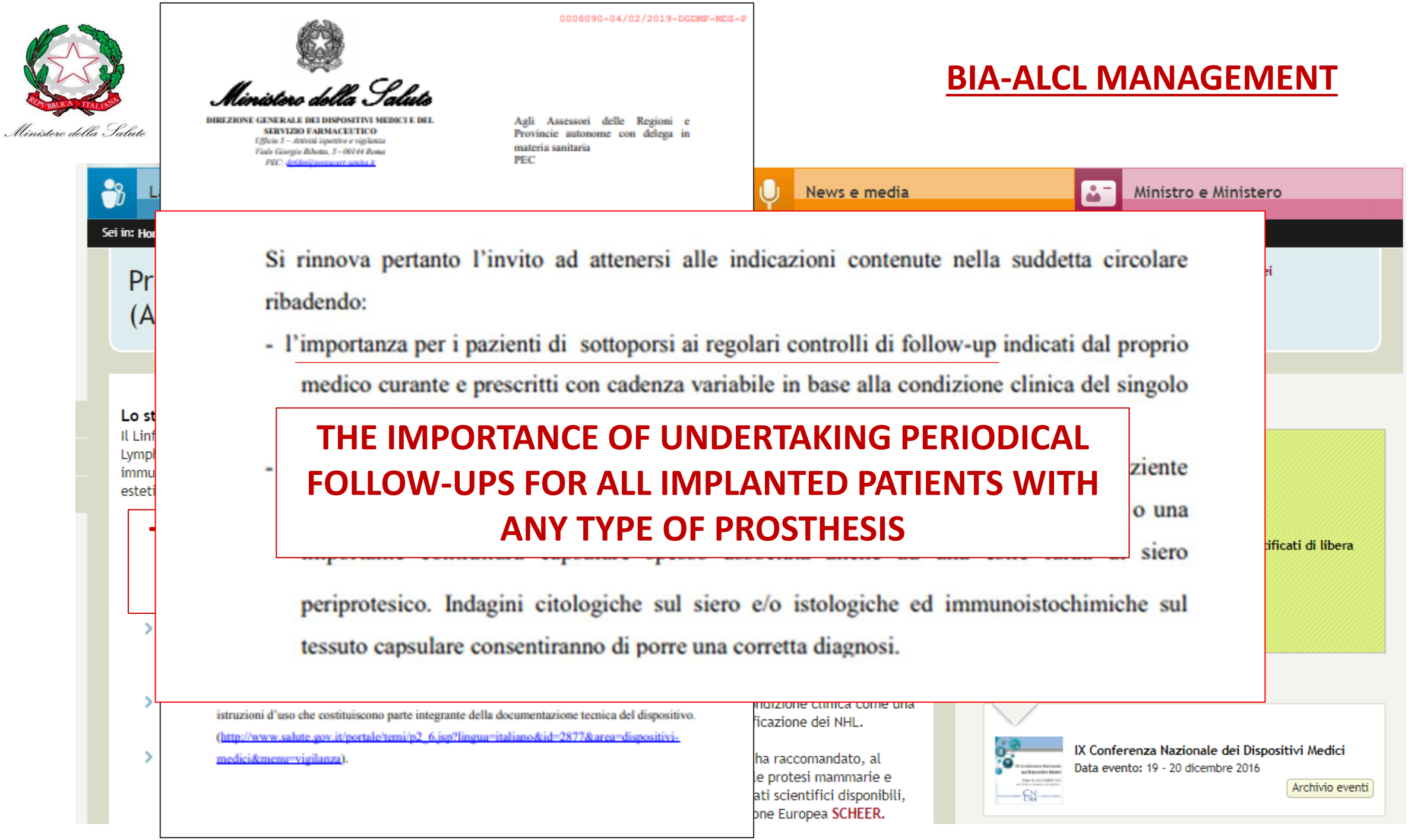
Se confermata la diagnosi, si dovrà prendere in considerazione per il paziente un approccio multidisciplinare con terapia idonea coerente con i dati presenti in letteratura. Per semplificare il processo di segnalazione dei nuovi casi di ALCL in pazienti portatrici di protesi mammarie, si potrà utilizzare il modulo pubblicato on-line sul sito del Ministero della Salute.

1. *WE GAVE DIRECTIONS ON HOW TO START PERFORMING A PROPER BIA-ALCL DIAGNOSIS*

2. MULTI-DISCIPLINARY APPROACH

3. *URGE NOTIFICATION OF NEW BIA-ALCL CASES*

BIA-ALCL MANAGEMENT



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DIREZIONE GENERALE DEI DISPOSITIVI MEDICI E DEL SERVIZIO FARMACEUTICO

Ufficio 5 – Attività ispettive e vigilanza

Viale Giorgio Ribotta, 5 - 00144 Roma

PEC: dgfdm@postacert.sanita.it

Agli Assessori delle Regioni e Provincie autonome con delega in materia sanitaria

PEC

Si rinnova pertanto l'invito ad attenersi alle indicazioni contenute nella suddetta circolare ribadendo:

- l'importanza per i pazienti di sottoporsi ai regolari controlli di follow-up indicati dal proprio medico curante e prescritti con cadenza variabile in base alla condizione clinica del singolo

THE IMPORTANCE OF UNDERTAKING PERIODICAL FOLLOW-UPS FOR ALL IMPLANTED PATIENTS WITH ANY TYPE OF PROSTHESIS

- siero

periprotesico. Indagini citologiche sul siero e/o istologiche ed immunoistochimiche sul tessuto capsulare consentiranno di porre una corretta diagnosi.

istruzioni d'uso che costituiscono parte integrante della documentazione tecnica del dispositivo. (http://www.salute.gov.it/portale/temi/p2_6.jsp?lingua=italiano&id=2877&area=dispositivi-medici&menu=vigilanza).

News e media

Ministro e Ministero

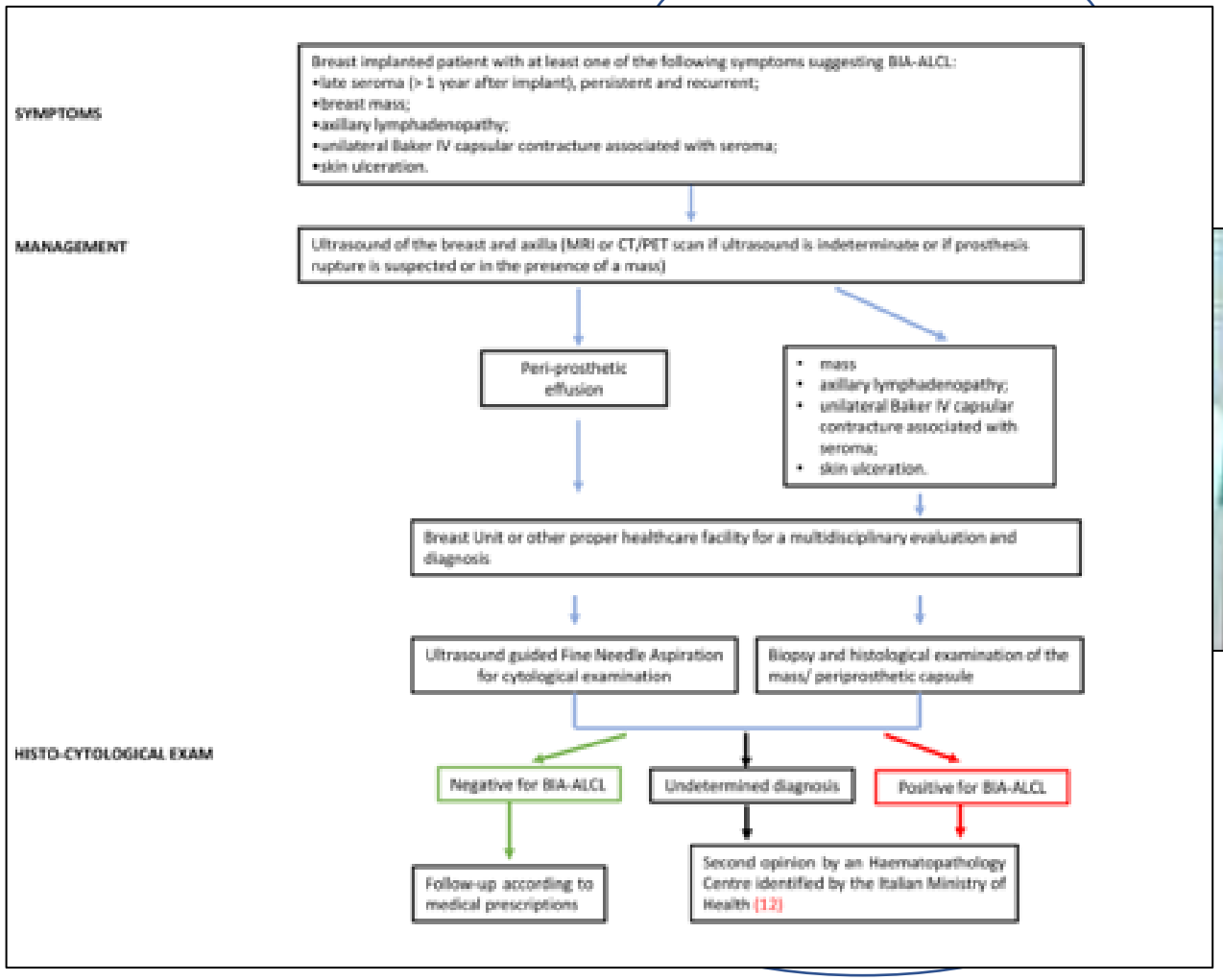
IX Conferenza Nazionale dei Dispositivi Medici

Data evento: 19 - 20 dicembre 2016

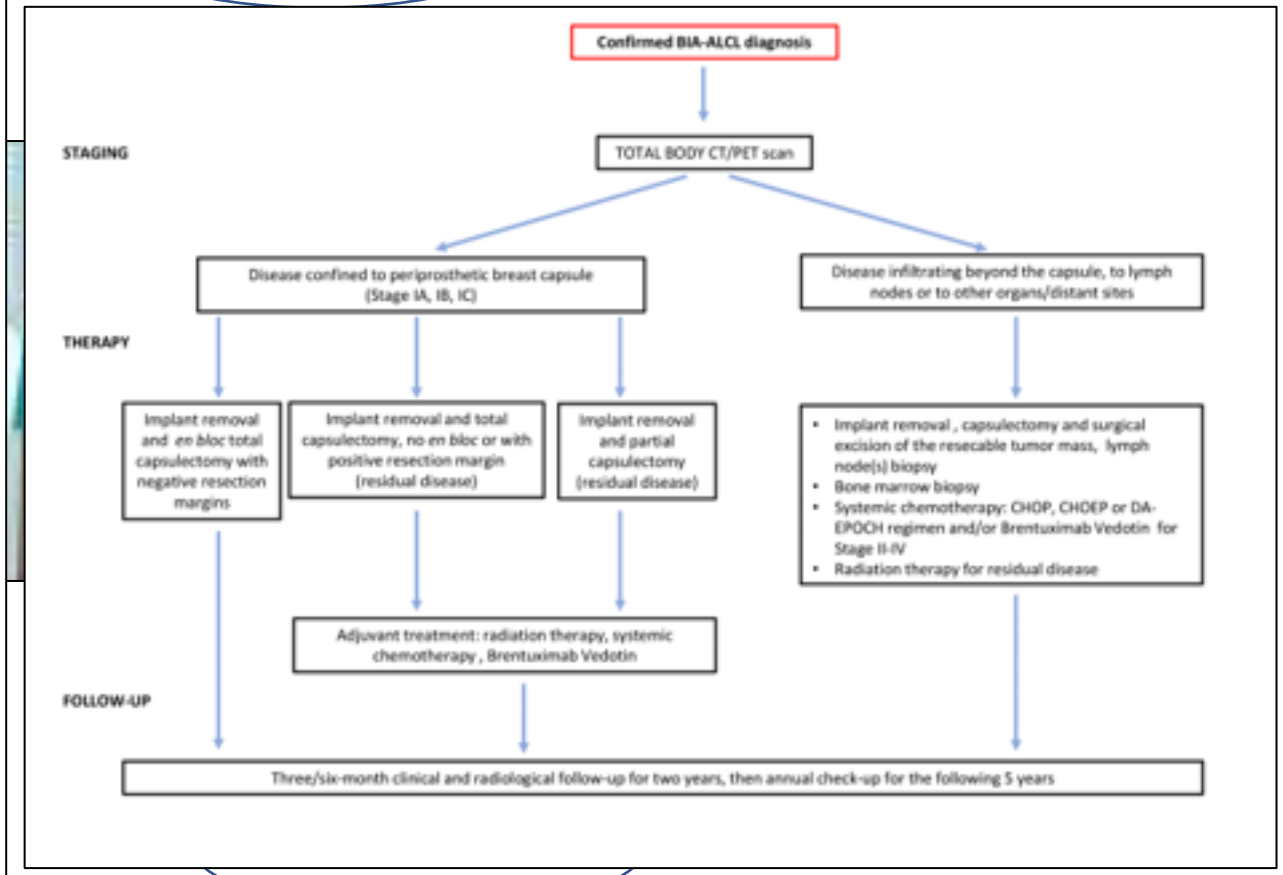
Archivio eventi

Ministero della Salute

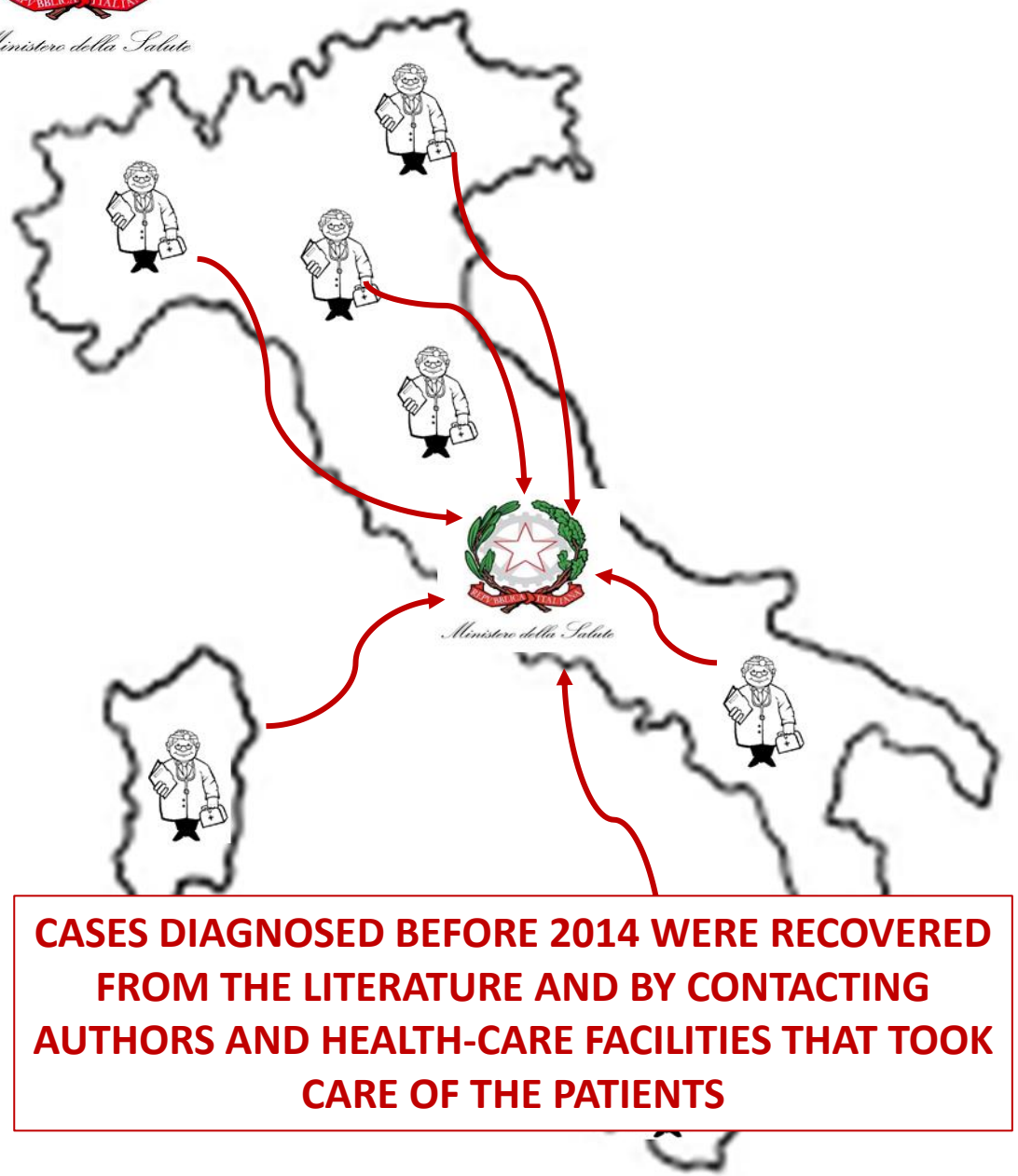
GUIDELINES ON BIA-ALCL DIAGNOSIS AND TREATMENT



PATHOLOGY



CENTRALIZED DATA COLLECTION



CASES DIAGNOSED BEFORE 2014 WERE RECOVERED FROM THE LITERATURE AND BY CONTACTING AUTHORS AND HEALTH-CARE FACILITIES THAT TOOK CARE OF THE PATIENTS

- Gender and Age
- Clinical history;
- Implant indication;
- Implantation date;
- Implant characteristics at the time of the onset of the symptoms;
- Previous implant history;
- Date of diagnosis;
- Implant characteristics at the time of diagnosis;
- Date of the onset of the symptoms;
- Symptoms;
- MDA TNM classification;
- MDA TNM staging;
- Treatment;
- Outcome.

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RESEARCH ON BIA-ALCL

BREAST

JANUARY 2018

22 Cases of Breast Implant–Associated ALCL: Awareness and Outcome Tracking from the Italian Ministry of Health

Antonella Campanale, M.D.
Rosaria Boldrini
Marcella Marletta, M.D.
Rome, Italy

Background: To date, 359 cases of anaplastic large cell lymphoma (ALCL) in women with breast implants (breast implant–associated ALCL [BIA-ALCL]) worldwide have been reported among more than 10 million patients who have received implants, but health care authorities suspect this is a possible underestimation, and the limited number of cases makes it difficult to clarify its cause. The General Directorate of Medical Devices and Pharmaceutical Services of the Italian Ministry of Health has examined and studied the Italian BIA-ALCL cases.

Methods: An official document has been diffused to all medical associations, aiming at encouraging all physicians to notify each BIA-ALCL case. A retrospective study has been performed on the notified BIA-ALCL cases collected in the database named Dispovigilance.

Results: Research on Dispovigilance returns a list of 22 BIA-ALCL cases. The mean patient age was 49.6 years (range, 30 to 71 years). The average time to the onset of the symptoms was 6.8 years (range, 1 to 22 years). The average time to diagnosis was 7.8 years (range, 4 to 22 years). The estimated incidence of the Italian BIA-ALCL cases related to 2015 is 2.8 per 100,000 patients.

Conclusions: The pathogenesis of BIA-ALCL remains unknown. The establishment of a national breast implant registry is needed to better understand some aspects of this disease. Future genetic studies on the population affected could clarify why only some patients with implants develop this disease. (*Plast. Reconstr. Surg.* 141: 11e, 2018.)

METHODOLOGY USED TO ESTIMATE THE INCIDENCE

Reply: 22 Cases of Breast Implant–Associated ALCL: Awareness and Outcome Tracking from the Italian Ministry of Health

Sir:

We are pleased that our article[1] generated such thoughtful inquiry and hope our correspondence will stimulate further interest, awareness, and promotion of notification of future breast implant–associated anaplastic large-cell lymphoma (BIA-ALCL) cases to the Italian Competent Authority. The incidence rate is the result of the division between new cases (numerator) occurring during a given period and population at risk (denominator) during the same period. We have considered 2015 as the period of reference and explained why in our article. There were seven new BIA-ALCL cases diagnosed in 2015. Therefore, seven was considered the numerator.

As the denominator, we considered all women with breast implants in 2015. To obtain this value, we extrapolated the following data:

Therefore, the K value was multiplied by 7. Thus, the denominator is equal to $K \times 7$, and the incidence rate in 2015 is equal to $7/K \times 7$.

Because the Italian Ministry of Health is aware of all breast implant sales data, our incidence has been estimated for any type of implanted device. Limitations of our estimated value related to the establishment of a national breast implant registry have been widely mentioned in our article.

A large heterogeneity of BIA-ALCL incidence rate has been reported in the literature[2,3] and, unfortunately, the authors did not give a detailed description of methodology used to define the denominator. Because we considered the importance of the denominator crucial, our article is the first to report accurately the methodology through which the denominator has been calculated and hope that future studies can apply a similar approach to come to a realistic estimation of the BIA-ALCL incidence.

DOI: 10.1097/PRS.0000000000004278

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Medical Device Vigilance System and Inspections
Italian Ministry of Health
Rome, Italy

INCIDENCE RATE IS CRITICAL IN THE RISK/ BENEFIT RATIO EVALUATION

of the X value is equal to Y, which represents the number of patients that received implants for reconstructive purposes. We assumed that reconstructive patients were mostly submitted to unilateral reconstruction. Moreover, 65 percent of the X value is equal to f, which represents the number of implanted devices for cosmetic purposes. However, we considered half of the f value, as each cosmetic patient mostly receives a pair of implants. According to these evaluations, the average number of implanted patients per year was: $Y + \frac{1}{2}f = K$.

2. Mean lifetime of the implant. We hypothesized that a patient is submitted to device removal or replacement over time. To estimate the mean implant lifetime, we have reviewed all data of the incidents that occurred in patients with breast implants and collected in the DISPOVIGILANCE database between 2012 and 2015. As a result, the mean implant lifetime was approximately 7 years.

REFERENCES

1. Campanale A, Boldrini R, Marletta M. 22 cases of breast implant–associated ALCL: Awareness and outcome tracking from the Italian Ministry of health. *Plast Reconstr Surg* 2018;141:11e–18e.
2. McGuire P, Reisman NR, Murphy DK. Risk factor analysis for capsular contracture, malposition, and late seroma in subjects receiving Natrelle 410 form-stable silicone breast implants. *Plast Reconstr Surg* 2017;139:1–9.
3. de Jong D, Vasmel WL, de Boer JP, *et al.* Anaplastic large-cell lymphoma in women with breast implants. *JAMA* 2008;300:2030–2035.
4. Doren EL, Miranda RN, Selber JC, *et al.* U.S. epidemiology of breast implant–associated anaplastic large cell lymphoma. *Plast Reconstr Surg* 2017;139:1042–1050.
5. Loch-Wilkinson A, Beath KJ, Knight RJW, *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;140:645–654.

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BIA-ALCL INCIDENCE

SIGNIFICANT VARIABILITY OF BIA-ALCL INCIDENCE 1/3.817 – 30.000

INCIDENCE RATE = The new cases occurring during a given time period / The population at risk during the same time period.

MANDATORY BREAST IMPLANT REGISTRY

DENOMINATOR
- IMPLANTS/YEAR
- IMPLANTS WITH AESTHETIC PURPOSES
- IMPLANTS WITH RECONSTRUCTIVE PURPOSES
- MEAN LIFE OF THE IMPLANT

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RESEARCH ON BIA-ALCL

BREAST

The Crucial Role of Surgical Treatment in BIA-ALCL Prognosis in Early- and Advanced-Stage Patients

Antonella Campanale, M.D.
Alessandra Spagnoli, Ph.D.
Lucia Lispi, S.D.
Rosaria Boldrini, S.D.
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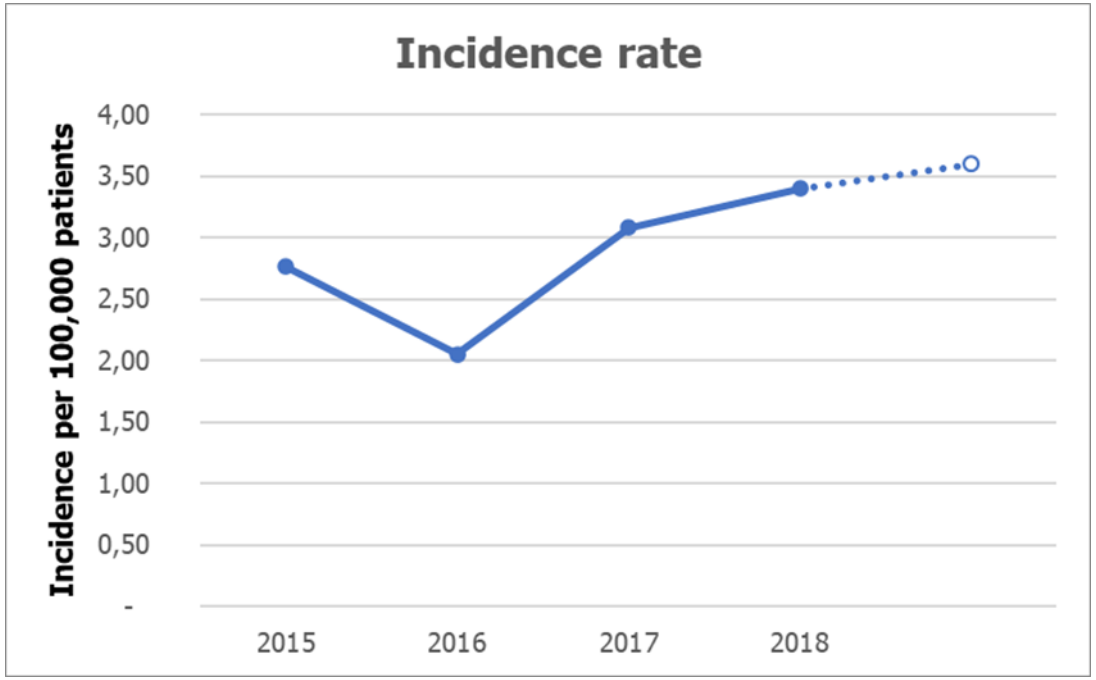
PATIENT SAFETY

Background: Studies on breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) are trying to optimize medical and surgical treatments for early and advanced stages of this disease. The aim of this article is to share the experience gathered on the authors' prospectively collected 46 well-documented cases.
Methods: Italian physicians are obliged to report BIA-ALCL cases to the Italian Ministry of Health. Because of this cooperation with health care professionals, the competent authority has coordinated and centralized the collection of information for each patient in 46 cases of BIA-ALCL. Statistical analyses with cumulative incidence and corresponding 95 percent confidence interval are provided for each year, dividing the number of new cases that occurred in a defined year and the population at risk of experiencing BIA-ALCL during the same year.
Results: The mean time to the onset of symptoms is reduced to 6.4 ± 3.77 years (range, 1 to 22 years). Increased knowledge has also shortened the average time to diagnosis, at 7.2 ± 3.71 years (range, 2 to 22 years). A late seroma appears in 91 percent of cases. The patient who died underwent limited surgery. The Italian incidence has been estimated as 2.8 per 100,000 patients receiving implants (95 percent CI, 0.88 to 4.84) in 2015; 2.1 (95 percent CI, 0.43 to 3.86) in 2016; 3.2 (95 percent CI, 1.11 to 5.31) in 2017; and 3.5 (95 percent CI, 1.36 to 5.78) in 2018.
Conclusion: Although the number of cases has risen slightly, BIA-ALCL is still a rare disease with a stable incidence, easily recognized and with a favorable prognosis also in advanced stages if complete surgical excision is performed. (*Plast. Reconstr. Surg.* 146: 530e, 2020.)

THE MONITORING INCIDENCE RATE PER YEAR IS FUNDAMENTAL



RARE DISORDER WITH AN INCIDENCE ABOUT 3/100.000 IMPLANTED PATIENTS

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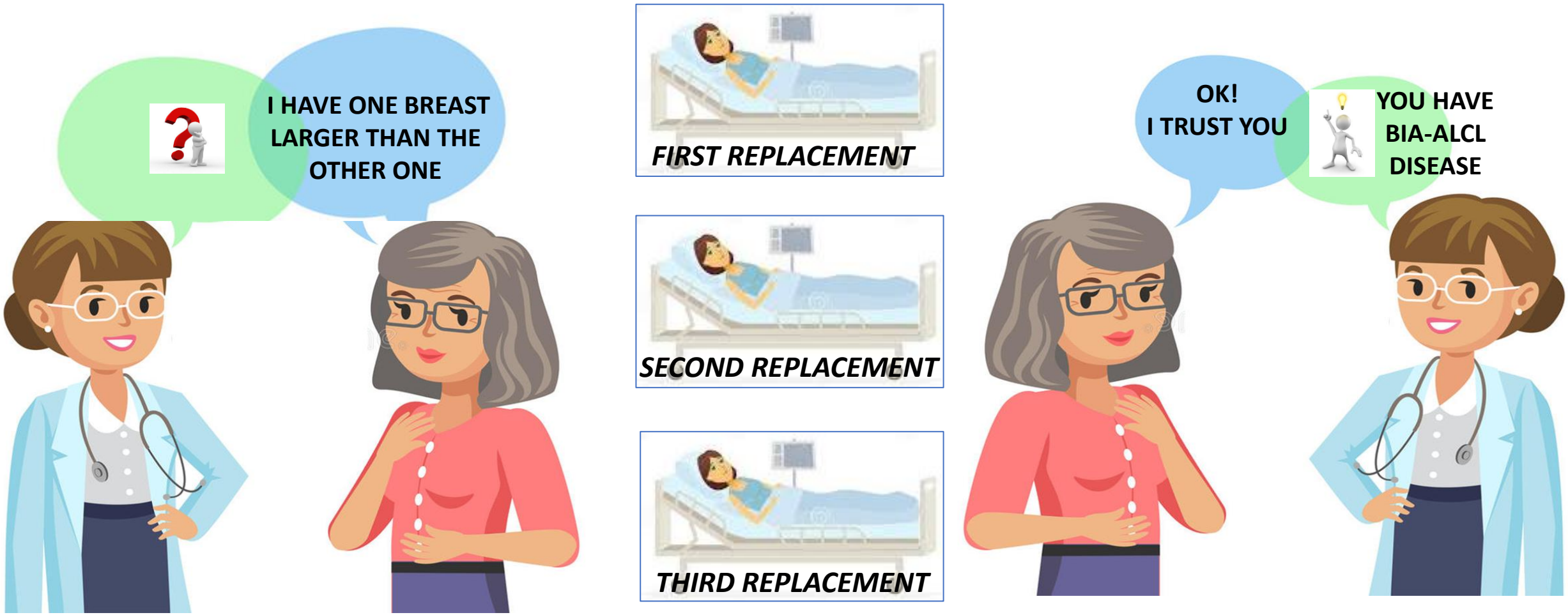
RECOVERING THE COMPLETE IMPLANT HISTORY IS FUNDAMENTAL TO UNDERSTAND THIS DISEASE



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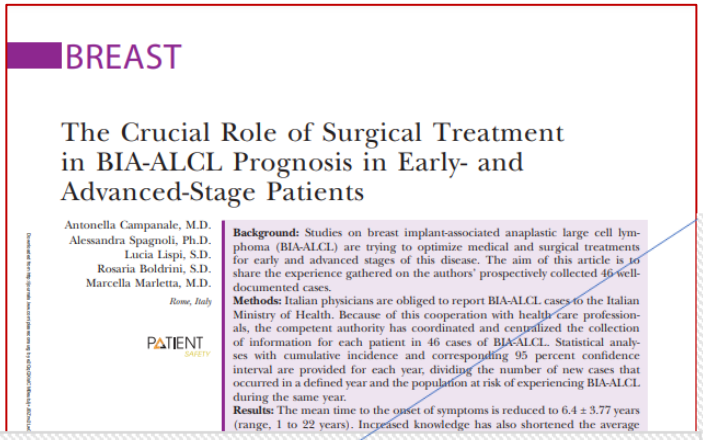
RESEARCH ON BIA-ALCL



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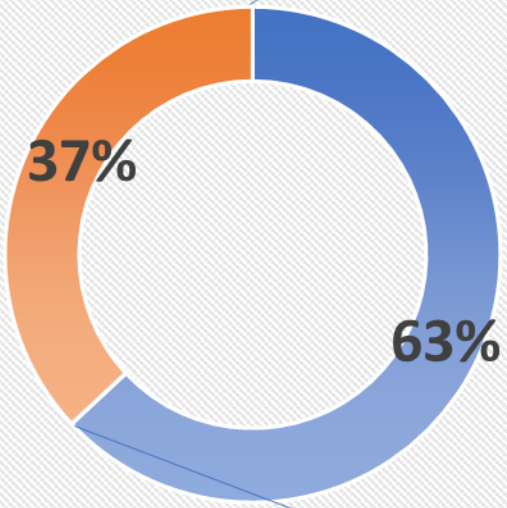
Results: The mean time to the onset of symptoms is reduced to 6.4 ± 3.77 years (range, 1 to 22 years). Increased knowledge has also shortened the average

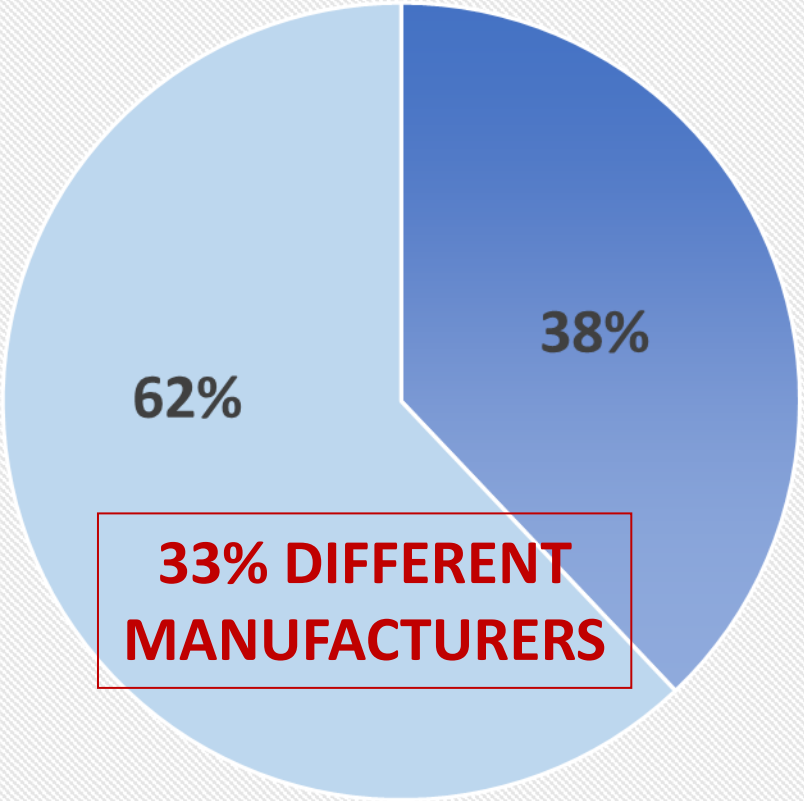
Implant History



YES

NO

Device Characteristics



33% DIFFERENT MANUFACTURERS

- Devices were SIMILAR at the onset of symptoms and at the time of diagnosis
- Devices were DIFFERENT at the onset of symptoms and at the time of diagnosis

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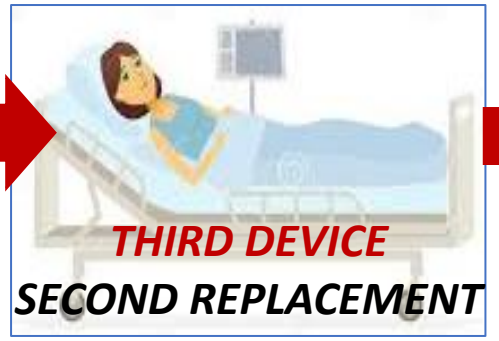
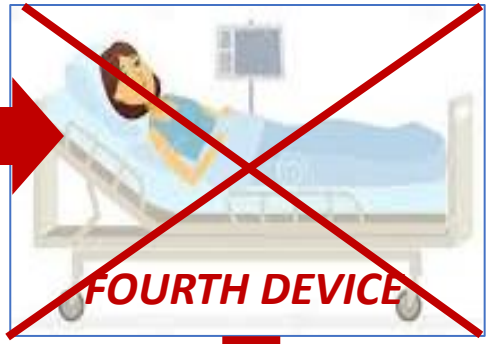
RESEARCH ON BIA-ALCL

BIA-ALCL SYMPTOMS





BIA-ALCL DIAGNOSIS

AUTHORS NEED TO RECOVER AND REVIEW THE IMPLANT HISTORY OF THEIR REPORTED CASES

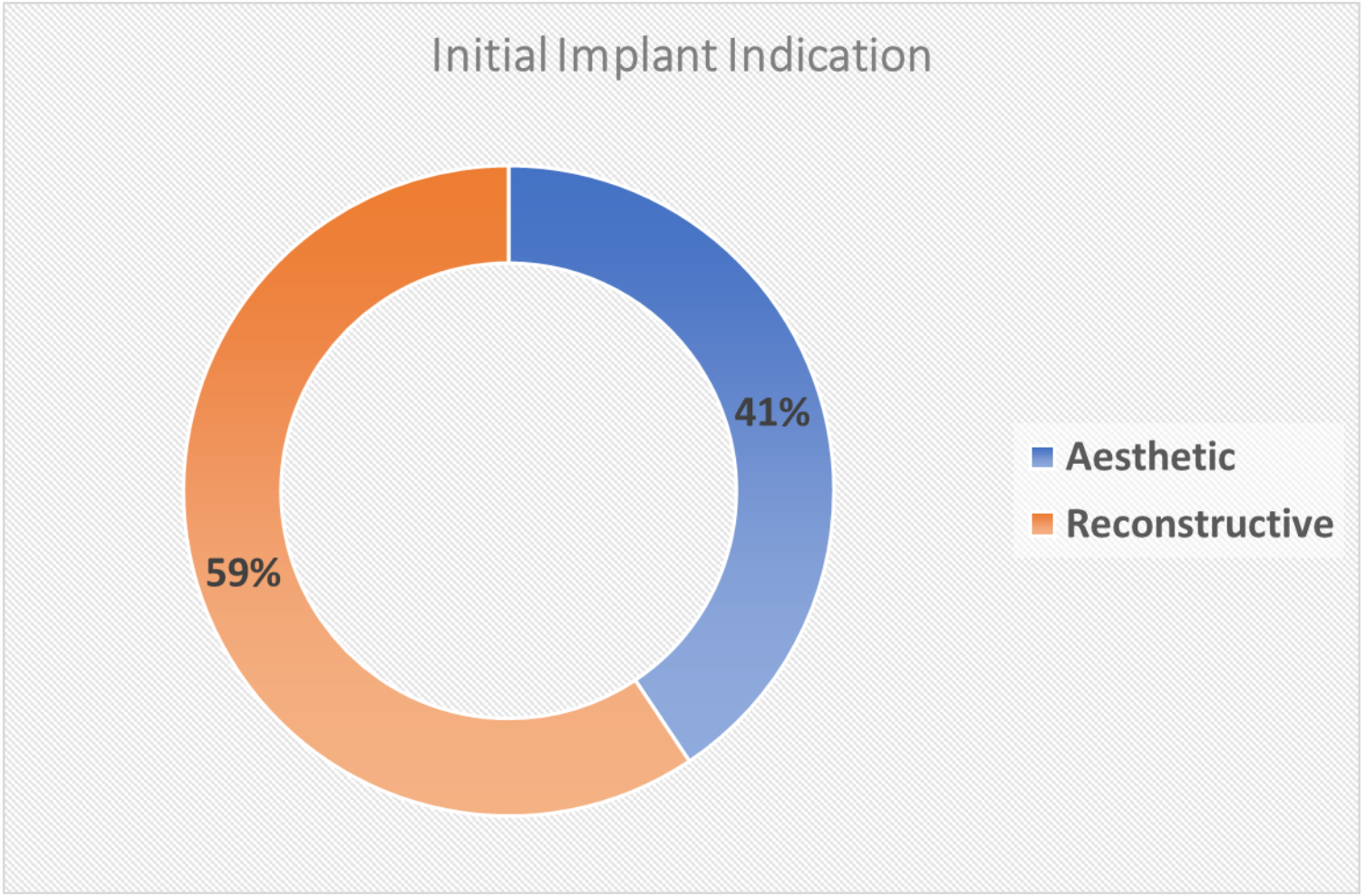
ITALIAN BIA-ALCL REPORT

January 2010 – September 30th 2020

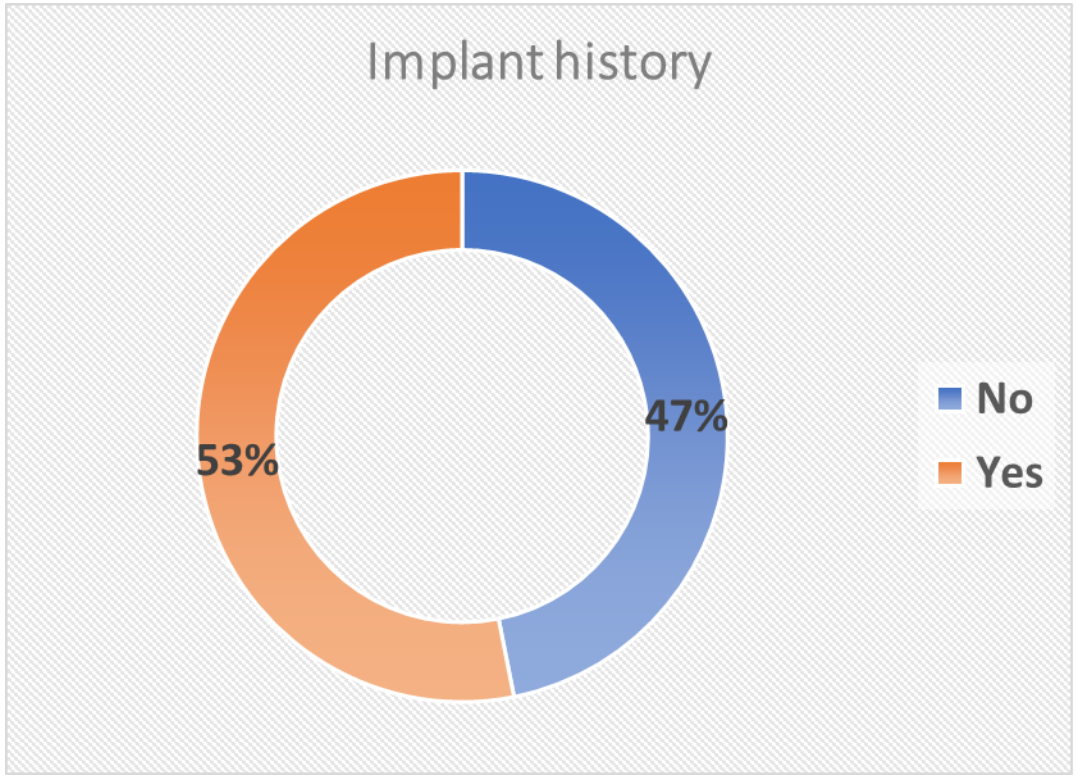
NOTIFIED CASES: **64 CASES**

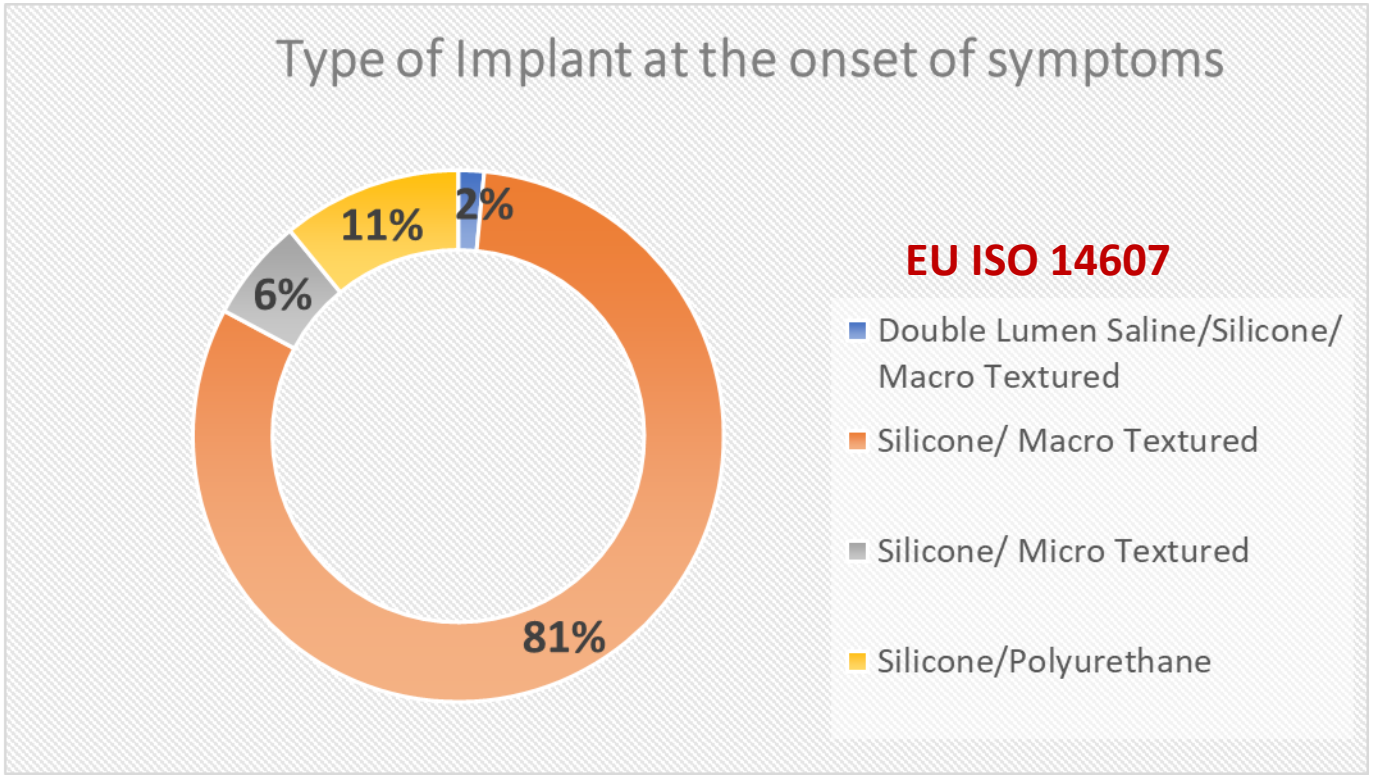
MEAN AGE: **54.7 YEARS**

MEAN TIME TO DIAGNOSIS: **7.7 YEARS**



ITALIAN BIA-ALCL REPORT - INVOLVED DEVICES AT THE ONSET OF THE SYMPTOMS

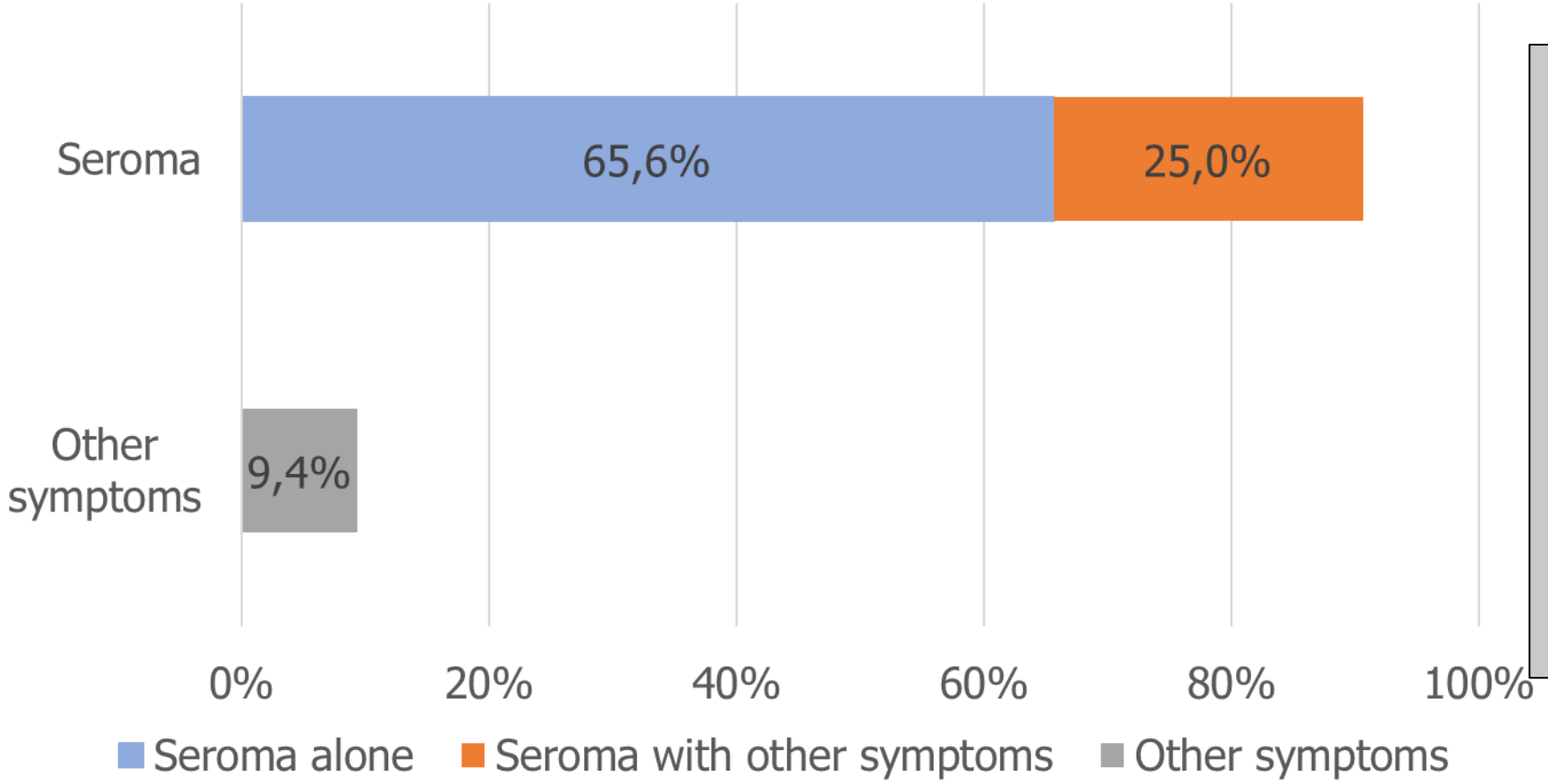




95% OF BREAST IMPLANTS SOLD ARE TEXTURED

ITALIAN BIA-ALCL REPORT - **SYMPTOMS**

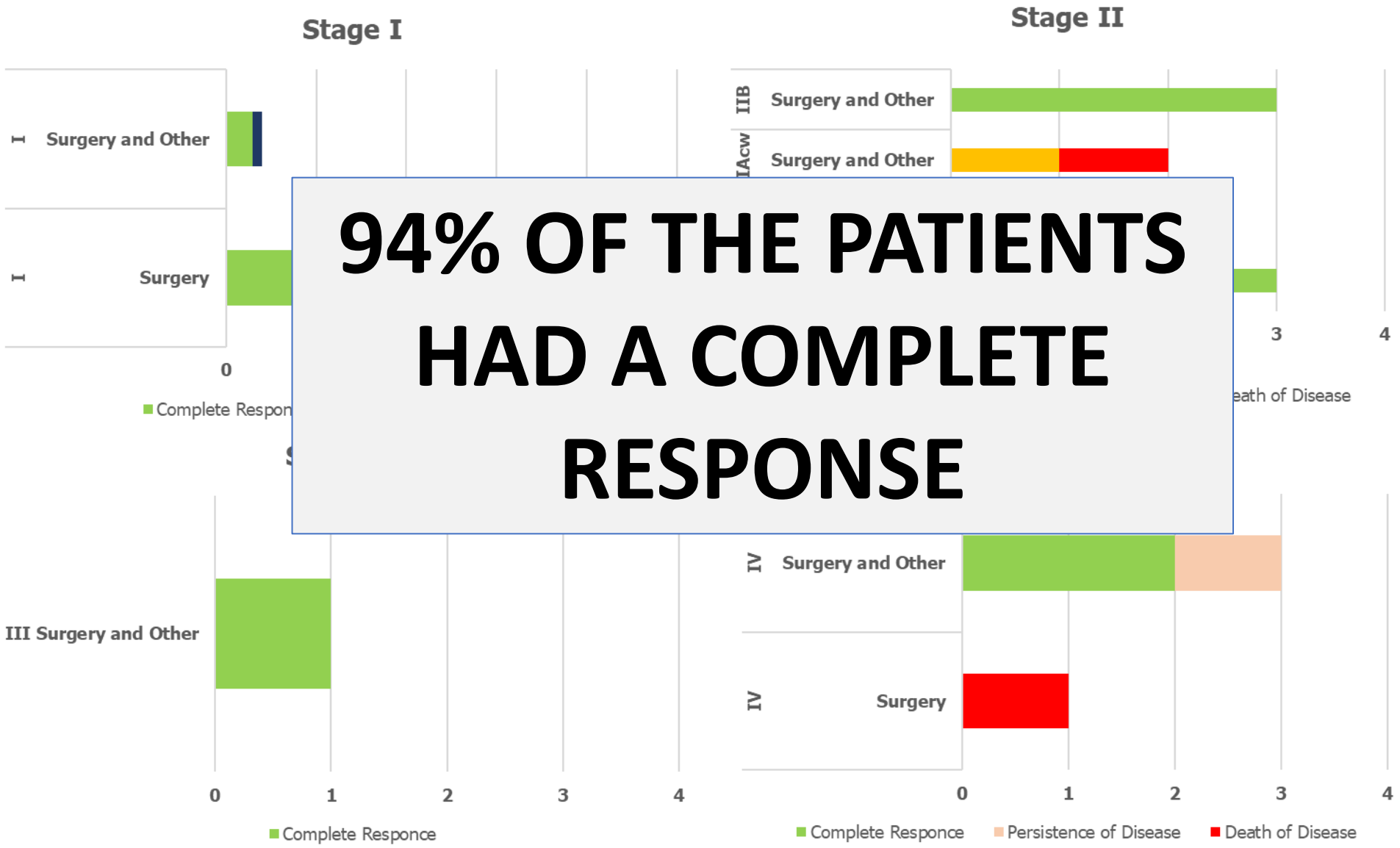
MEAN TIME TO THE ONSET OF SYMPTOMS: 7.1 YEARS



OTHER SYMPTOMS:

- *Mass*
- *Capsular contracture*
- *Itch*
- *Erythema*
- *Breast pain*
- *Fever/ Wheight loss / Astenia*

ITALIAN BIA-ALCL REPORT - OUTCOMES ACCORDING WITH STAGE AND TREATMENT ADOPTED



94% OF THE PATIENTS HAD A COMPLETE RESPONSE

MEDIAN FOLLOW UP TIME OF 30 MONTHS

OTHER TREATMENT:

- *Pharmacological Therapy*
- *Radiotherapy*

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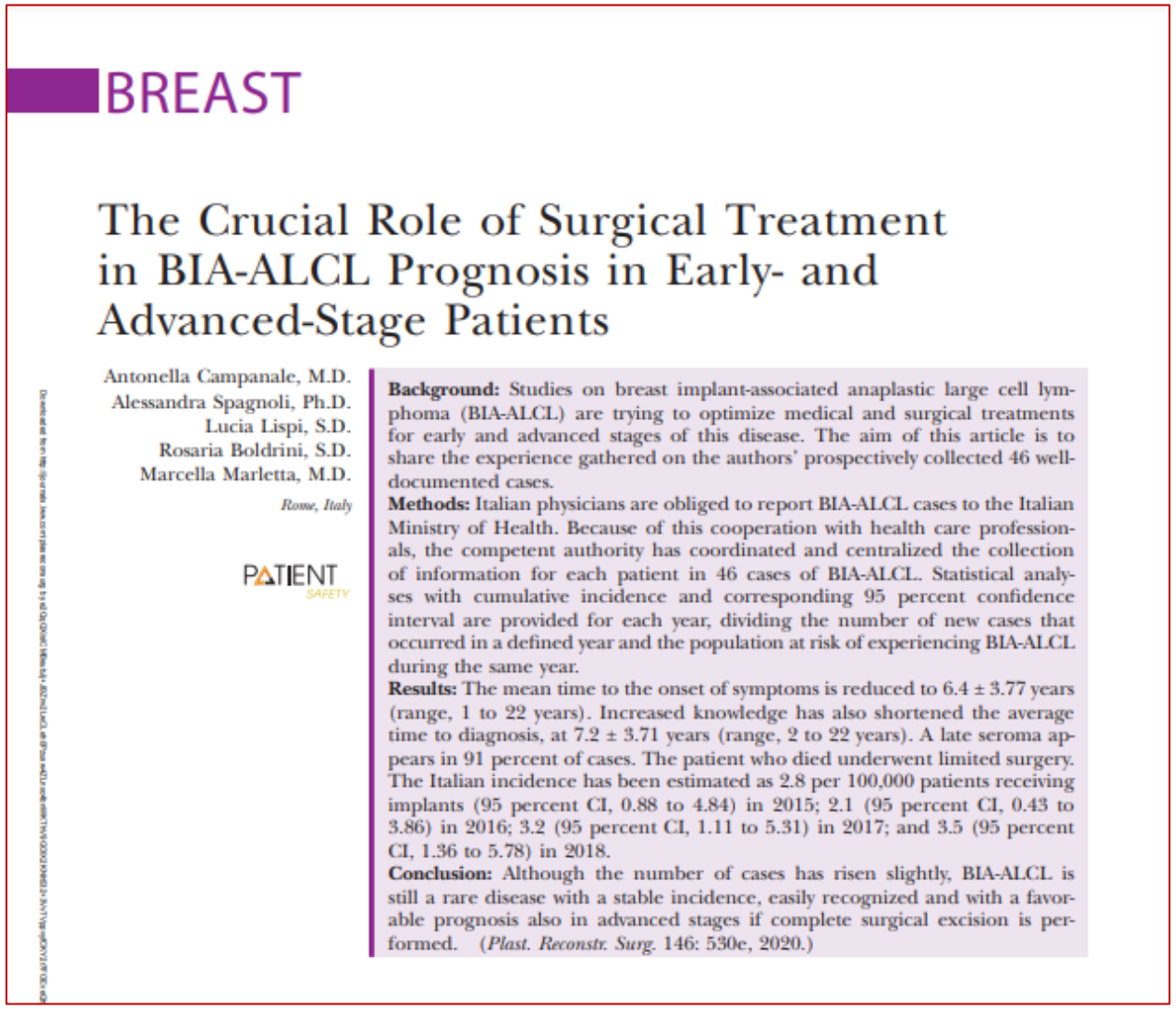
BIA-ALCL REPORT - OUTCOMES ACCORDING WITH STAGE AND TREATMENT ADOPTED



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- **BIA-ALCL LIKE A SOLID TUMOR**

- **RADICAL SURGICAL TREATMENT IS THE KEY FACTOR THAT CAN LEAD THIS DISORDER TO A COMPLETE REMISSION, EVEN IN PATIENTS IN ADVANCED STAGES**

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STATE OF ART ON BIA-ALCL ISSUE

- BIA-ALCL IS A RARE DISEASE WITH A FAVORABLE PROGNOSIS
- MULTIFACTORIAL ETIOPATHOGENESYS TO BE STILL CLARIFIED

GENETIC STUDIES MUST BE SUPPORTED

- BIA-ALCL HAVE BEEN ADDED TO THE RISKS OF THIS TYPE OF SURGERY
- AWARENESS FOR BOTH PHYSICIANS AND PATIENTS MUST BE CONSTANTLY PROMOTED
- ALL TYPE OF BREAST IMPLANTS MUST BE MONITORIZED
- SMOOTH IMPLANTS CANNOT BE EXCLUDED BY THE PATHOGENESIS OF THIS DISEASE

[c] In the 28 cases of smooth implants, 10 have unknown prior history of implants, 8 have a history of at least one textured implant, 9 have a history of prior implants with unknown texture, and 1 has a history of one smooth implant and no known textured implant. It should be noted that many MDR reports do not contain information, or contain incomplete information, on the prior implant history of the patient. Therefore, this section may be updated as new information emerges. As of January 5, 2020, there are no reports of cases associated with tissue expanders.

NO DATA ABOUT POST MARKET SURVILLANCE OF SMOOTH IMPLANTS WE HAVE

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STATE OF ART ON BIA-ALCL ISSUE

COMPETENT AUTHORITIES SIDE

- MANDATORY BREAST IMPLANT REGISTRY HAS TO BE PROMOTED AND SUPPORTED
- PREMARKET STUDIES HAVE TO BE ENHANCED
- THE CLASSIFICATION OF BREAST IMPLANT SURFACE HAS TO BE IMPROVED

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COMMENTS ON THE PRELIMINARY OPINION ON THE SAFETY OF BREAST IMPLANTS IN RELATION TO ANAPLASTIC LARGE CELL LYMPHOMA

- **ALL ACTIONS UNDERTAKEN AND THE SCIENTIFIC EVIDENCE AQUIRED** BY THE ITALIAN COMPETENT AUTHORITY **HAVE BEEN TOTALLY IGNORED** WHILE OTHER PAPERS, PUBLISHED AHEAD OF PRINT , AND WHICH DO NOT FALL WHITHIN THE CONSIDERED PERIOD HAVE SURPRISINGLY BEEN ADDED TO THE REFERENCES;

DESPITE TO WHAT HAS BEEN REPORTED:

- **CLINICAL INDICATION** FOR THE USE OF ONE TYPE OF BREAST IMPLANT VERSUS ANOTHER **DEPENDS** ON THE PREOPERATIVE CLINICAL CONDITION FOR BOTH AESTHETIC AND RECONSTRUCTIVE PURPOSES (*paragraph 2.1 page 9, line 17-20 and paragraph 4.1 page 13 line 46-49)*

- **ANATOMICAL SHAPED /TEXTURED BREAST IMPLANTS CANNOT BE ALWAYS REPLACED** BY OTHER PROCEDURES IN AESTHETIC SURGERY

- **AFT AS AN ALTERNATIVE TO BREAST IMPLANT AUGMENTATION IS OFTEN NOT POSSIBLE AS IT DEPENDS ON THE AMOUNT OF FAT TISSUE AVAILABLE** FOR MULTIPLE SURGICAL SESSIONS (*paragraph 4.3 page 17, line 27-28)*

- **AUTOLOGOUS RECONSTRUCTION REQUIRES A GREAT SURGICAL EXPERTISE** AND PHISICIANS ARE NOT ALWAYS ABLE TO PERFORM IT. THERE IS THE HIGH RISK THAT MANY PATIENTS DO NOT RECEIVE RECONSTRUCTION

THANK YOU

A. Campanale, L. Lispi, A. Iachino

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