Advances in Malignant lymphomas:
The case of extranodal and T-cell lymphomas

Santiago de Chile
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Rare primary extranodal DLBCL: Primary Breast Lymphoma (PBL)

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FONDAZIONE FIL ITALIANA LINFOMI

Disclosures

Research Support (institution)	**Mundipharma**
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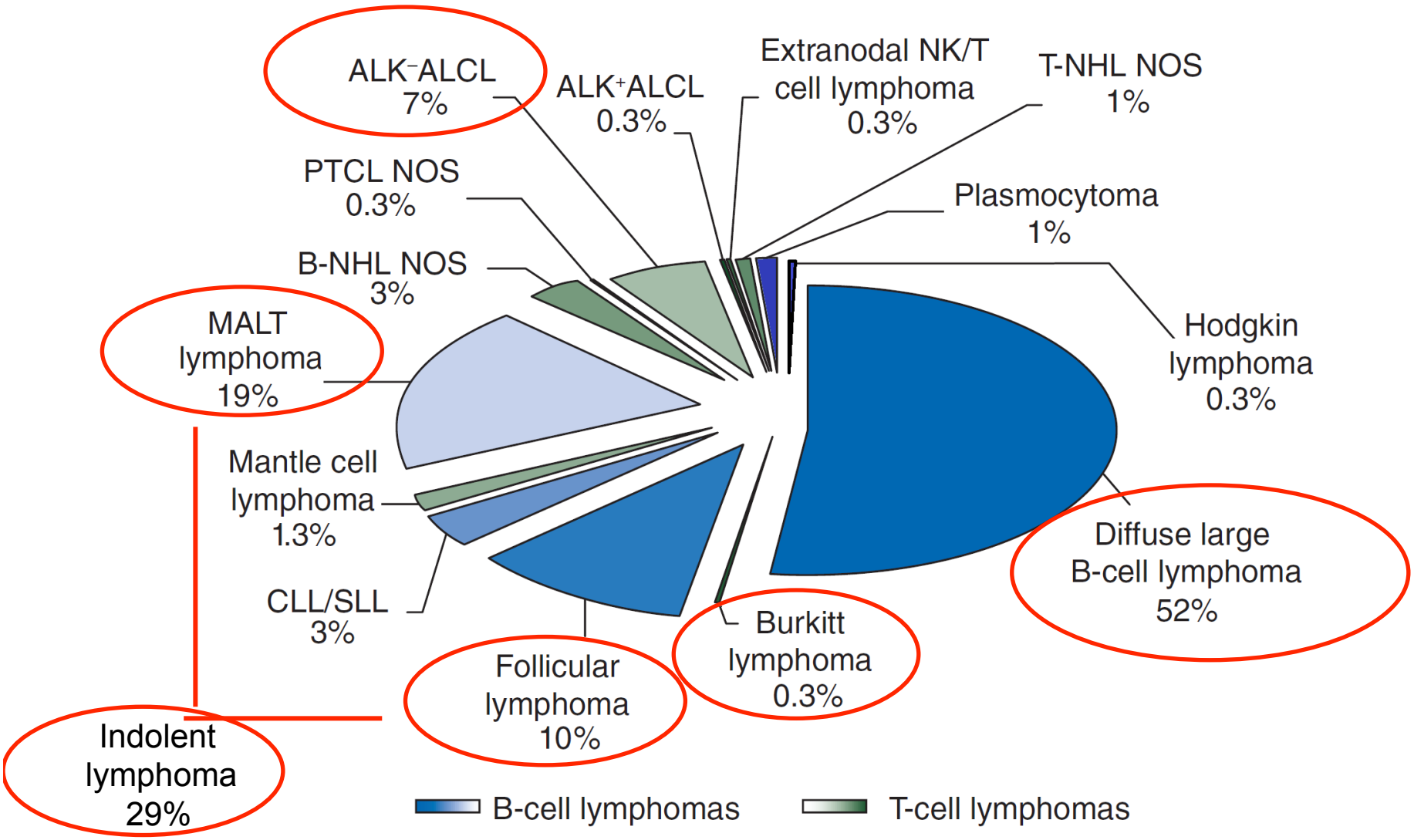
Major Stockholder	-
Speakers Bureau	-
Speakers Honoraria	**Celgene, Janssen, Mundipharma, Pfizer, Roche**
Scientific Advisory Board	**Celgene, Janssen, Pfizer, Roche, Teva, Servier**

Primary breast lymphoma (PBL)

- 0.01–0.5% of all malignant breast tumors
- 0.7% of all lymphomas (*French Lymphopath Network)*
- 92% B-cell lymphomas and 6% ALK-negative ALCL associated with breast implants

Primary Breast Lymphoma (PBL)



Histologic subtypes of the 300 cases in the French Lymphopath network from 2010 to 2014. (Laurent *et al.* Ann Oncol 2016)

Primary breast lymphoma (PBL)

- Primary indolent breast lymphoma (MZL, FL)
- Primary diffuse large B cell breast lymphoma (DLBCL)
- Breast implant-associated ALCL (BIA-ALCL)

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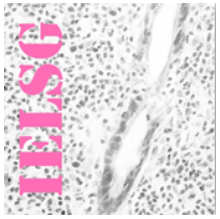
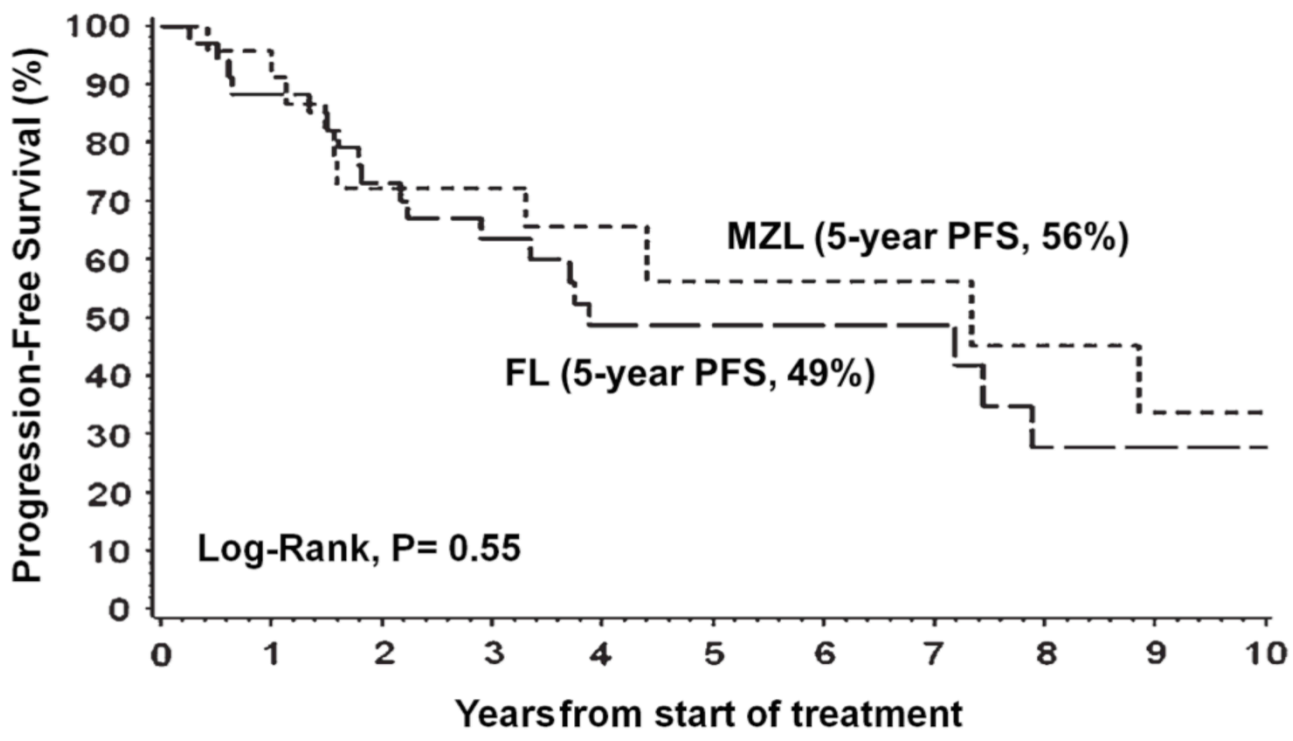


IELSG survey of primary indolent lymphomas of the breast

- 60 patients, 36 FL and 24 MZL
- Median follow-up time, 44 months
- Stage I_E or II_E in 57 patients
- Stage IV_E in 3 patients due to bilateral involvement
- Surgery in 67%, chemotherapy and radiotherapy alone in 42% or in combination in 52% of patients as first-line treatment
- No significant differences in outcome by treatment type
- ORR 98%, with 93% CR rate

G. Martinelli et al. Ann Oncol 2009;20:1993-9

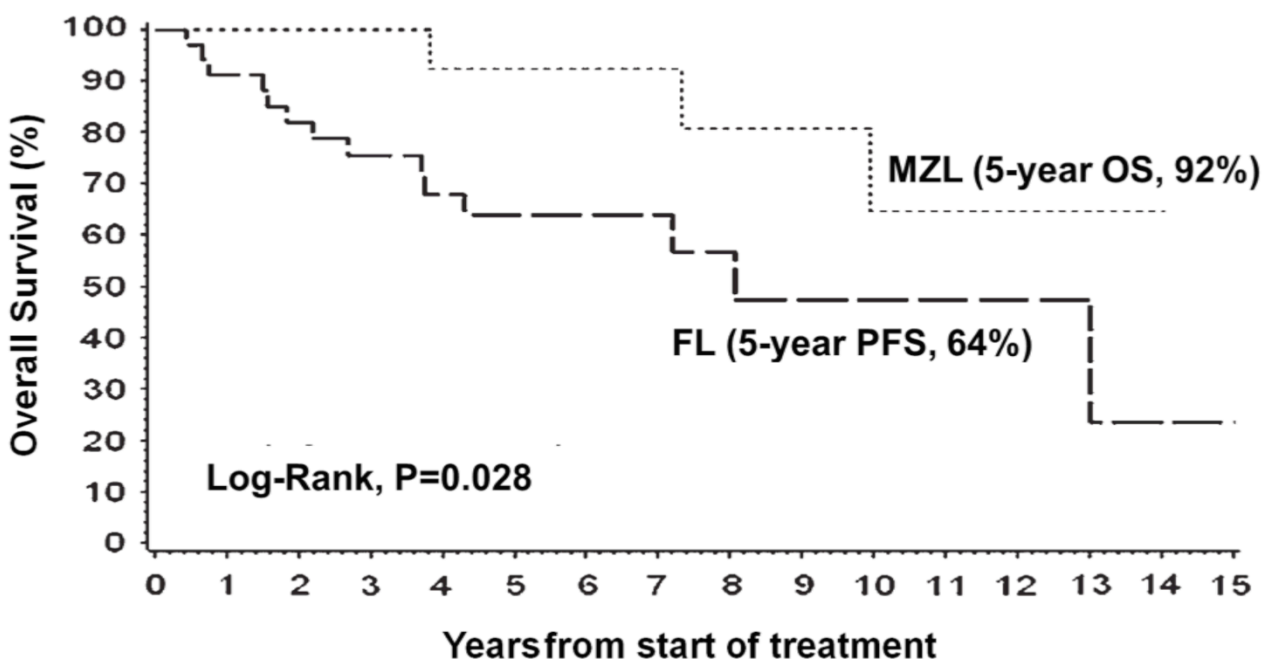
Long term outcomes of primary indolent lymphomas of the breast



- Relapses were mostly in distant sites (18/23 cases)
- No patients relapsed within RT fields

G. Martinelli et al. Ann Oncol 2009;20:1993-9

Long term outcomes of primary indolent lymphomas of the breast



- indolent behaviour of MZL, comparable to other primary extranodal MZL
- Inferior outcomes of FL when compared with limited-stage nodal FL cases

G. Martinelli et al. Ann Oncol 2009;20:1993-9

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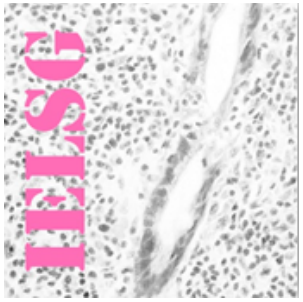


original article

Annals of Oncology 19: 233–241, 2008
doi:10.1093/annonc/mdm471
Published online 11 October 2007

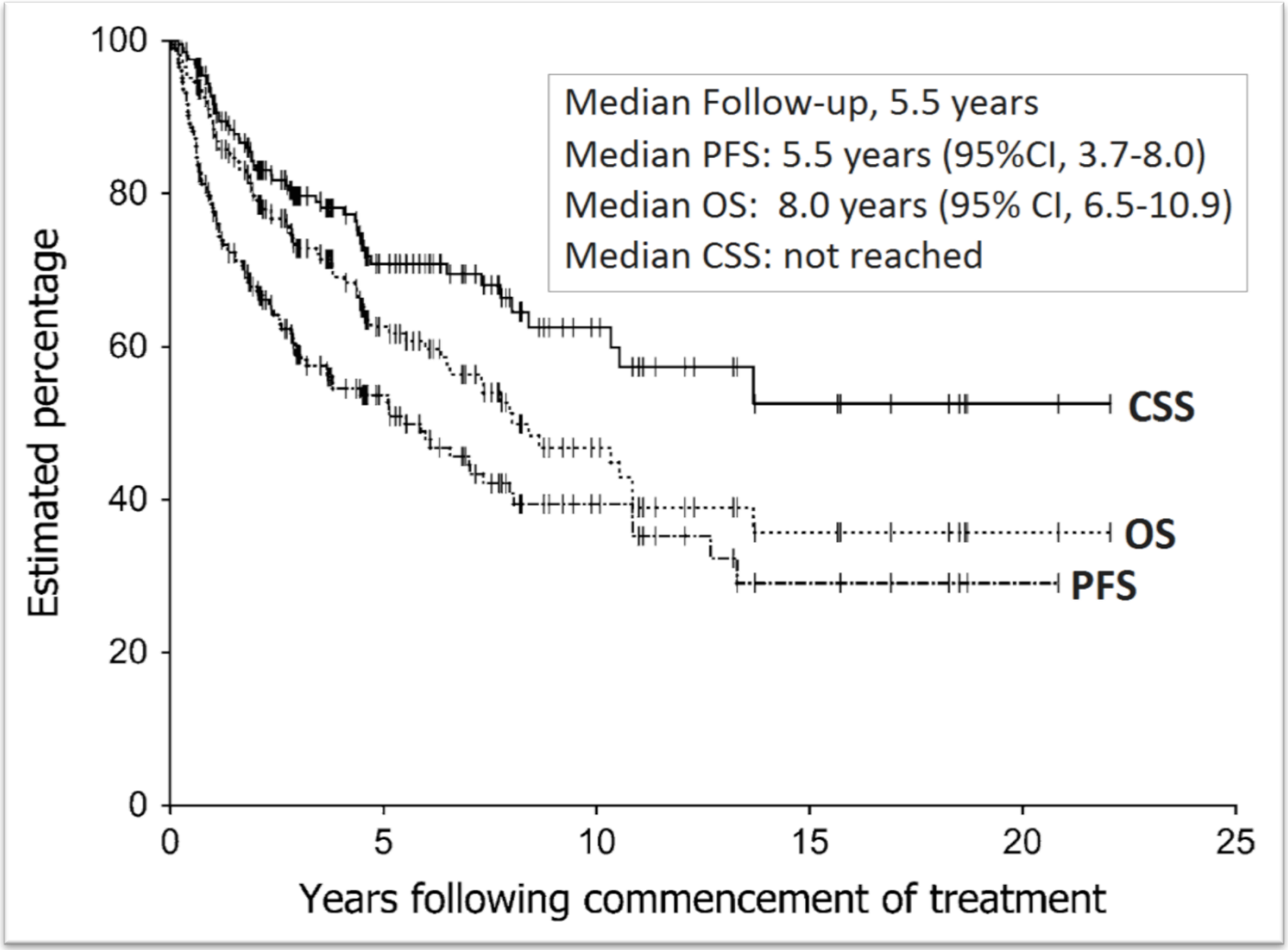
Primary diffuse large B-cell lymphoma of the breast: prognostic factors and outcomes of a study by the International Extranodal Lymphoma Study Group

G. Ryan[1]*, G. Martinelli[2], M. Kuper-Hommel[3], R. Tsang[4], G. Pruneri[2], K. Yuen[1], D. Roos[5], A. Lennard[6], L. Devizzi[7], S. Crabb[8], D. Hossfeld[9], G. Pratt[10], M. Dell'Olio[11], S. P. Choo[12], R. G. Bociek[13], J. Radford[14], S. Lade[1], A. M. Gianni[5], E. Zucca[15], F. Cavalli[15] & J. F. Seymour[1]

- 204 patients diagnosed from 1980 to 2003
- Unilateral disease, 95%
- Median age, 64 years
- 76 progressions
- 81 deaths (54 due to lymphoma)
- No benefit from mastectomy (vs. biopsy or lumpectomy only)

G. Ryan et al. Ann Oncol 2008;19:233-241

IELSG retrospective survey of primary DLBCL of the breast



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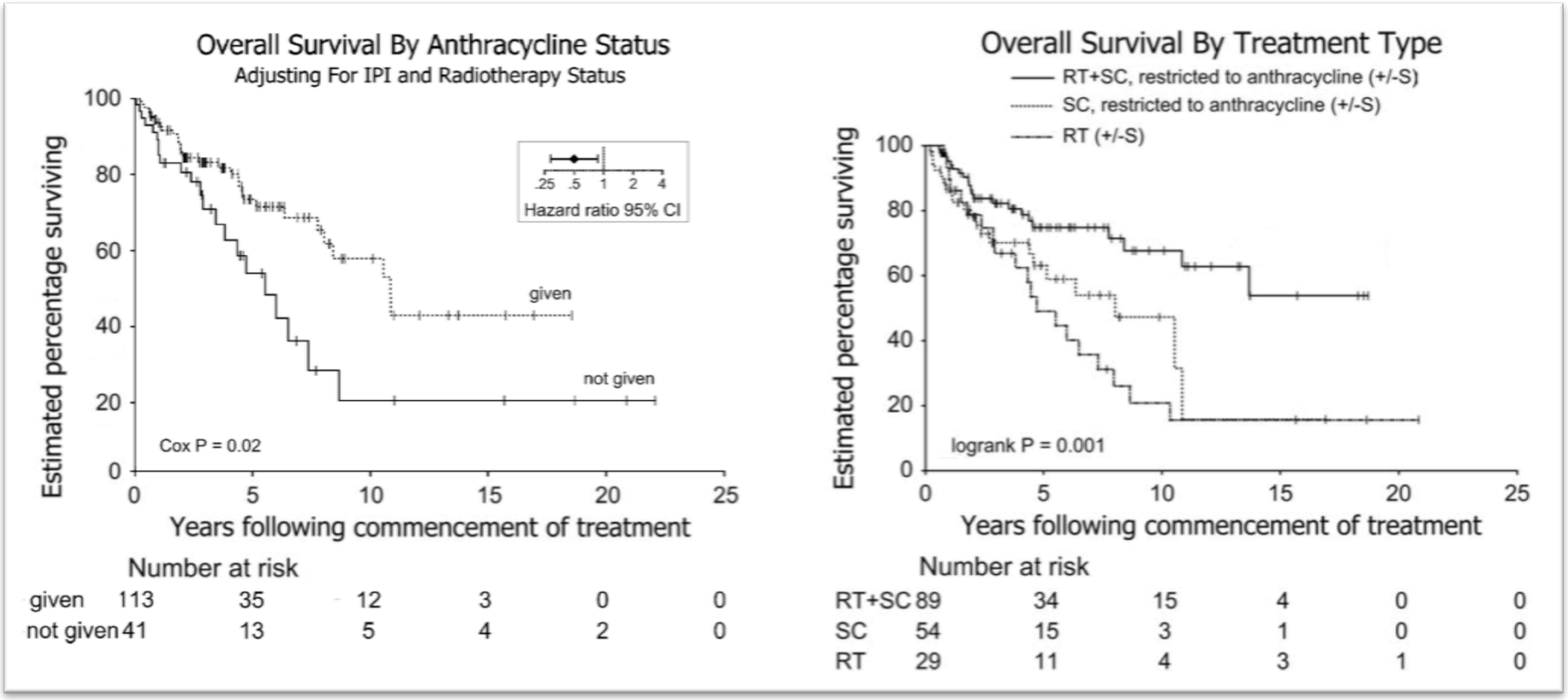

The combination of limited surgery, anthracycline-containing chemotherapy and involved-field RT produced the best outcome in the pre-rituximab era

G. Ryan et al. Ann Oncol 2008;19:233-241

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journal homepage: www.elsevierhealth.com/journals/ctrv

Tumor Review

Primary breast lymphoma

Chan Y. Cheah [a,b,1], Belinda A. Campbell [b,c,2], John F. Seymour [a,b,*]

[a] Department of Haematology, Peter MacCallum Cancer Centre, East Melbourne, Melbourne, Victoria, Australia
[b] University of Melbourne, Parkville, Melbourne, Victoria, Australia
[c] Division of Radiation Oncology, Peter MacCallum Cancer Centre, East Melbourne, Melbourne, Victoria, Australia

2014

Study	Year	Type	*n* DLBCL (% of series)	Chemotherapy	Rituximab (%)	RT (%)	PFS (%)
Ryan	2008	Retrospective	204 (100)	70% Anthracycline based	0%	64	5-Year PFS 54
Hosein	2014	Retrospective	76 (100)	CHOP 72%	62%	63	5-Year PFS 66
Yhim	2010	Retrospective	49 (100)	97% Anthracycline based	62%	31	5-Year PFS 54
Caon	2012	Retrospective	28 (87*)	CHOP 73%*	43%*	50*	5-Year 'distant control' 70*
Validire	2008	Retrospective	38 (84)	80% "anthracycline based"	10%	71	5-Year PFS 54**
Zhao	2011	Retrospective	28 (90)	CHOP 74%	% not stated	65	5-Year PFS 57**
Guo	2008	Retrospective	37 (82)	CHOP-like 79%	14%	49	5-Year PFS 35**
Aviles	2005	Prospective	96	RT v CHOP v combined			10-Year PFS 50, 56, 83
Aviles	2007	Prospective	32	R-CEOP Q14	100%	100	3-Year PFS 75

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2014

Adverse prognostic factors

Overall Survival

- High IPI
- Bilateral involvement
- Stage IIE vs IE
- Tumor size > 4,5 cm
- Received mastectomy
- No anthracycline CHT
- < 4 cycles CHT
- No radiation

Progression Free Survival

- High IPI
- Bilateral involvement
- Stage IIE vs IE
- Tumor size > 4,5 cm
- No anthracycline CHT
- < 4 cycles CHT

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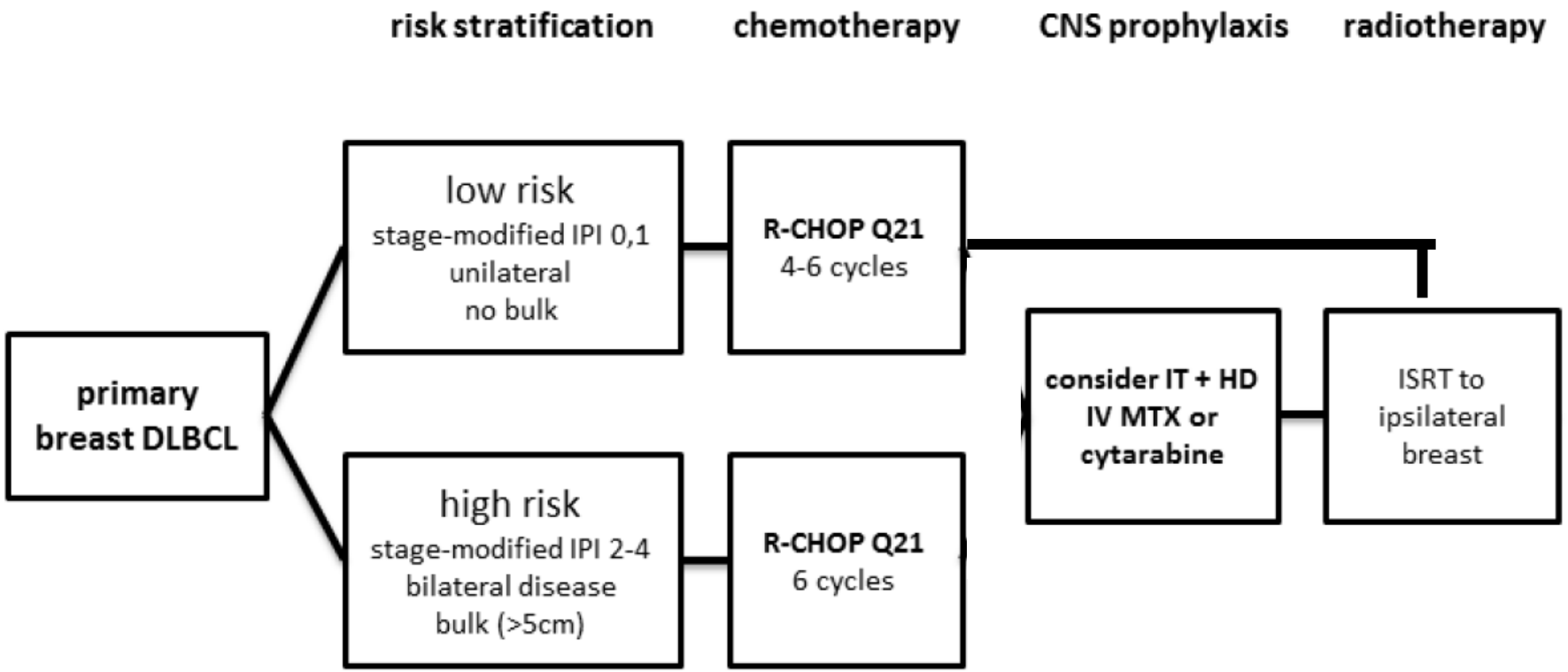
2014

CNS risk and role of CNS prophylaxis

- CNS relapse in 5-16% of cases
- potential risk factors include bilateral involvement, advanced stage, and bulky tumor (>5cm)
- most CNS relapses occurr <2 years after therapy
- controversial role of CNS-directed intratecal prophylaxis
- most CNS relapses in brain parenchyma (high-dose IV MTX or Ara-C may be more effective than IT prophylaxis)

Proposed treatment algorithm for patients with primary breast DLBCL



CY Cheah, et al. Cancer Treatment Reviews . 2014; 40(8):900-8

Primary breast lymphoma (PBL)

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- Breast implant-associated ALCL (BIA-ALCL)

Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder

Anja C Roden[1], William R Macon[1], Gary L Keeney[1], Jeffrey L Myers[2], Andrew L Feldman[1] and Ahmet Dogan[1]

[1]*Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA and* [2]*Department of Pathology, University of Michigan Health System, Ann Arbor, MI, USA*

Non-Hodgkin lymphomas of the breast are rare, encompassing approximately 0.04–0.5% of all malignant breast tumors, and the vast majority are B-cell lymphomas. In contrast, lymphomas of T-cell phenotype have been rarely reported and some of these have been in close proximity to a breast implant. In our consultation practice, we have identified four patients with primary T-cell anaplastic large-cell lymphoma presenting adjacent to silicone or saline breast implants. All patients presented with seroma and neoplastic cells were identified in suspension in the serous fluid without solid tissue invasion. Three patients had no evidence of systemic disease (stage 1E), and one patient was not staged. The mean age of the patients was 46 years (range, 34–59 years). In all patients, the neoplastic cells had a T-cell phenotype, expressed CD30, cytotoxic granule-associated proteins, EMA and clusterin, and were anaplastic lymphoma kinase-1-negative. Clonal T-cell receptor γ-chain gene rearrangements were identified in three patients. All patients underwent capsulectomy with removal of the implant. One patient subsequently received chemotherapy and radiation therapy, and another was treated with radiation alone. The third patient received no further therapy and the fourth patient has been recently diagnosed. After a mean time of 13 months (range, 9–20 months), all three patients with follow-up were alive and well without any recurrence or systemic disease. Although the follow-up time was relatively short, our series and other reported cases suggest that primary anaplastic large-cell lymphoma adjacent to breast implants is an indolent T-cell lymphoproliferative disorder.

Modern Pathology 2008

Plastic and Reconstructive Surgery • March 2015

SPECIAL TOPIC

Anaplastic Large Cell Lymphoma Occurring in Women with Breast Implants: Analysis of 173 Cases

Garry S. Brody, M.D., M.Sc.
Dennis Deapen, Dr.Ph.
Clive R. Taylor, M.D., D.Phil.
Lauren Pinter-Brown, M.D.
Sarah Rose House-Lightner, B.A.
James S. Andersen, M.D.
Grant Carlson, M.D.
Melissa G. Lechner, Ph.D.
Alan L. Epstein, M.D., Ph.D.

Los Angeles and Duarte, Calif.; Atlanta, Ga.; and Boston, Mass.

Background: The first silicone breast implant was inserted in 1962. In 1997, the first case of anaplastic large cell lymphoma (ALCL) in association with a silicone breast implant was reported. The authors reviewed 37 articles in the world literature reporting on 79 patients and collected another 94 unreported cases as of the date of submission.

Methods: The world literature was reviewed. Missing clinical and laboratory information was solicited from the authors and treating physicians. As several different specialties were involved, information was not in one place. Many (but not all) authors and treating physicians were responsive, resulting in incomplete data.

Results: ALCL lesions first presented as late peri-implant seromas, a mass attached to the capsule, tumor erosion through the skin, in a regional node, or discovered during revision surgery. The clinical course varied widely from a single positive cytology result followed by apparent spontaneous resolution, to disseminated treatment-resistant tumor and death. There was no preference for saline or silicone fill or for cosmetic or reconstructive indications. Where implant history was known, the patient had received at least one textured-surface device. Extracapsular dissem-

Breast implant-associated ALCL (BIA-ALCL)

Histology

- proliferation of large anaplastic cells

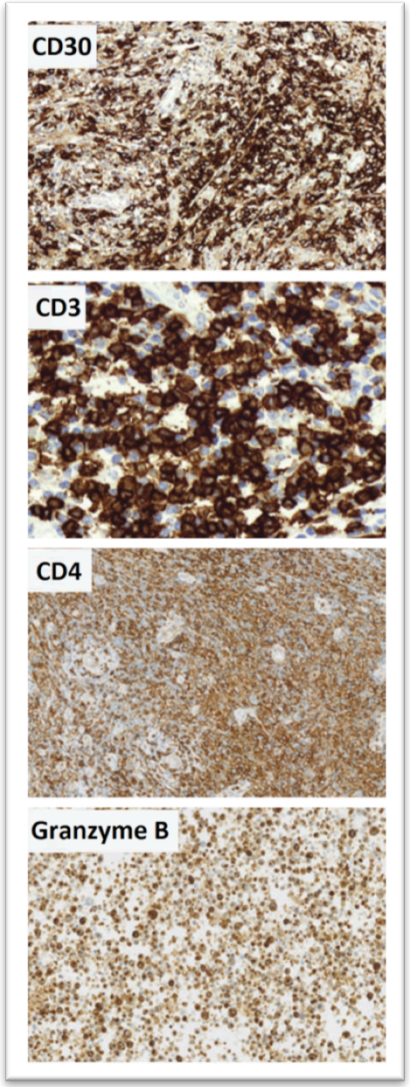
Immunophenotype

- strongly CD30-positive
- always ALK-negative
- incomplete T-cell phenotype
- activated cytotoxic profile
- most often CD4 and CD43-positive
- TCRβF1 and TCRγ usually negative
- IRF4/MUM1, pSTAT3 and PAX5 usually positive
- consistently EBV-negative

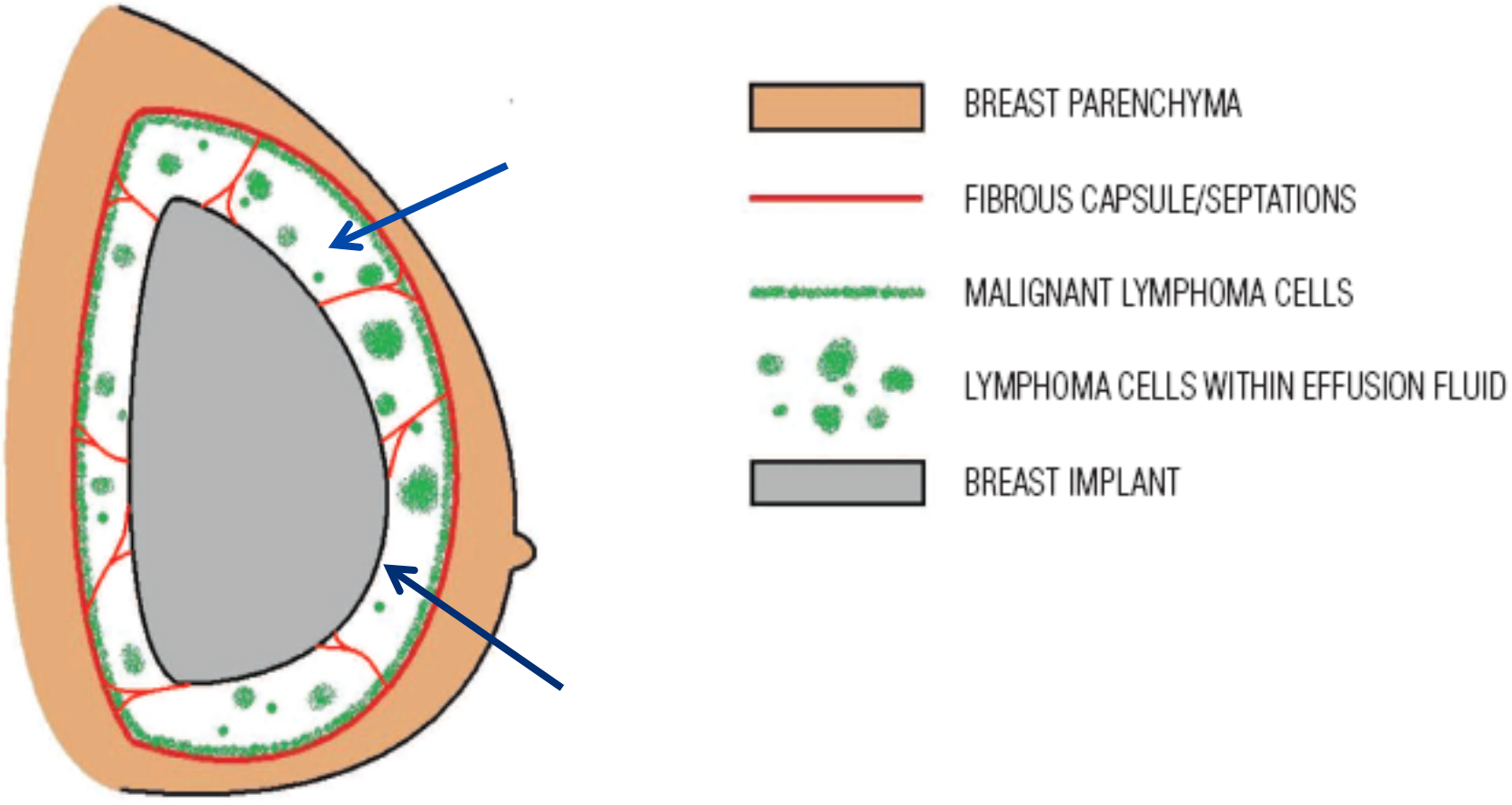
Clonal gene rearrangements

- TCRG usually rearranged
- TCRB in half of the cases

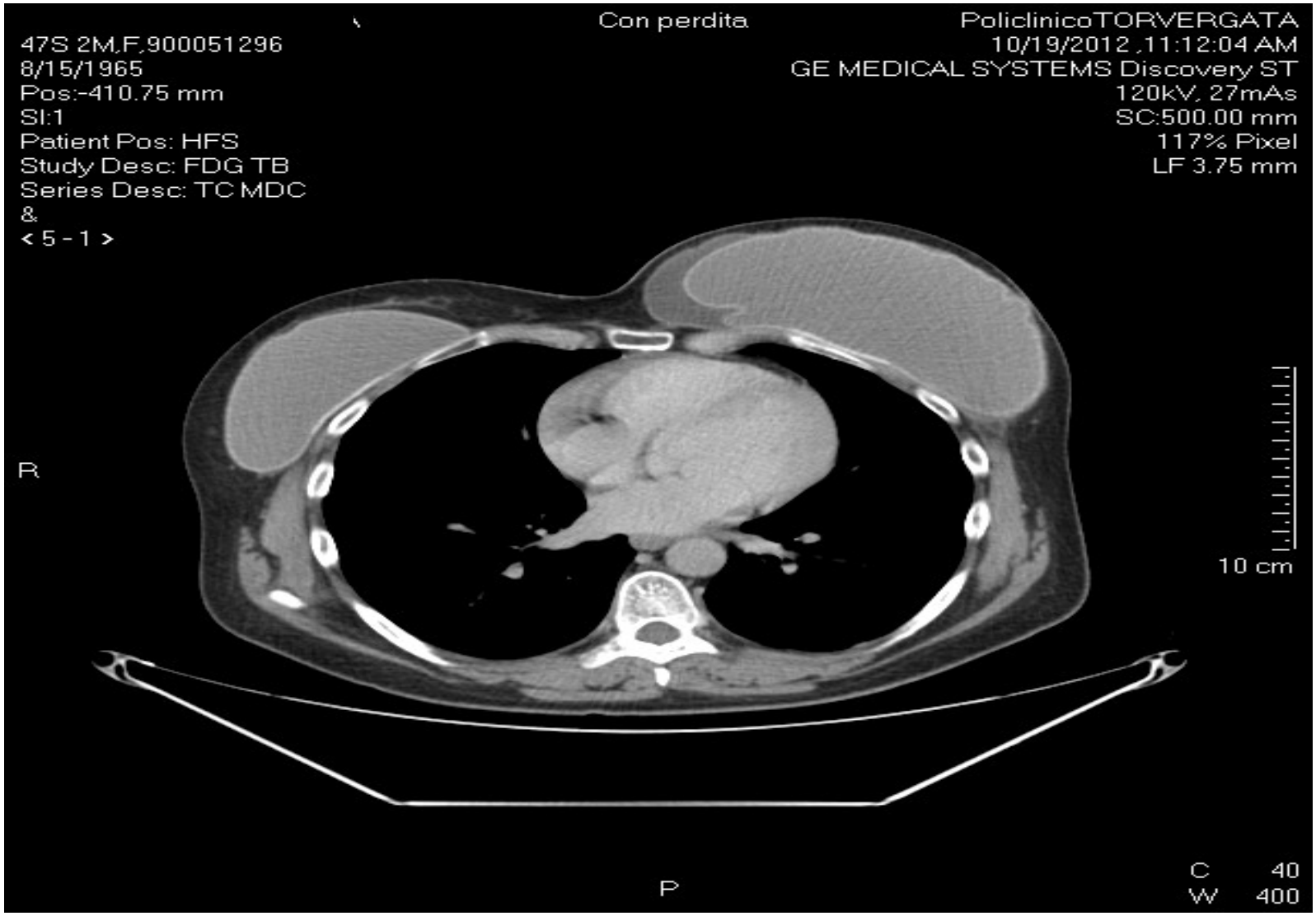
Laurent et al. Ann Oncol 2016



Breast implant-associated ALCL:
schematic representation of seroma in situ BIA-ALCL



Seroma of the breast: CT finding



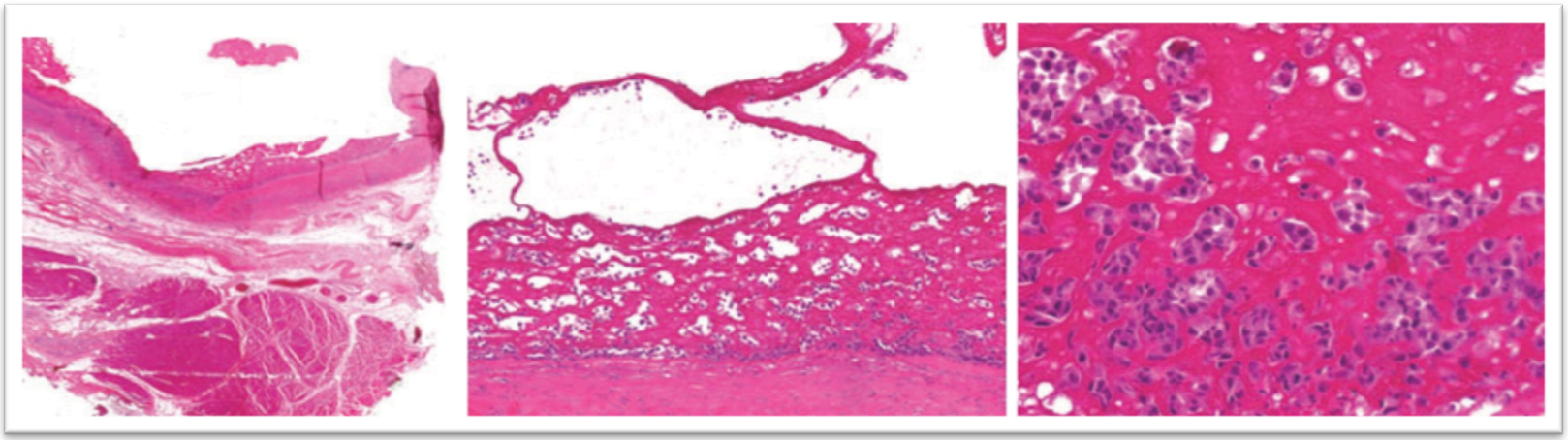
Breast implant-associated ALK-neg ALCL

Pathological variants

- in situ implant-associated ALCL
- infiltrative implant-associated ALCL

In situ implant-associated ALCL

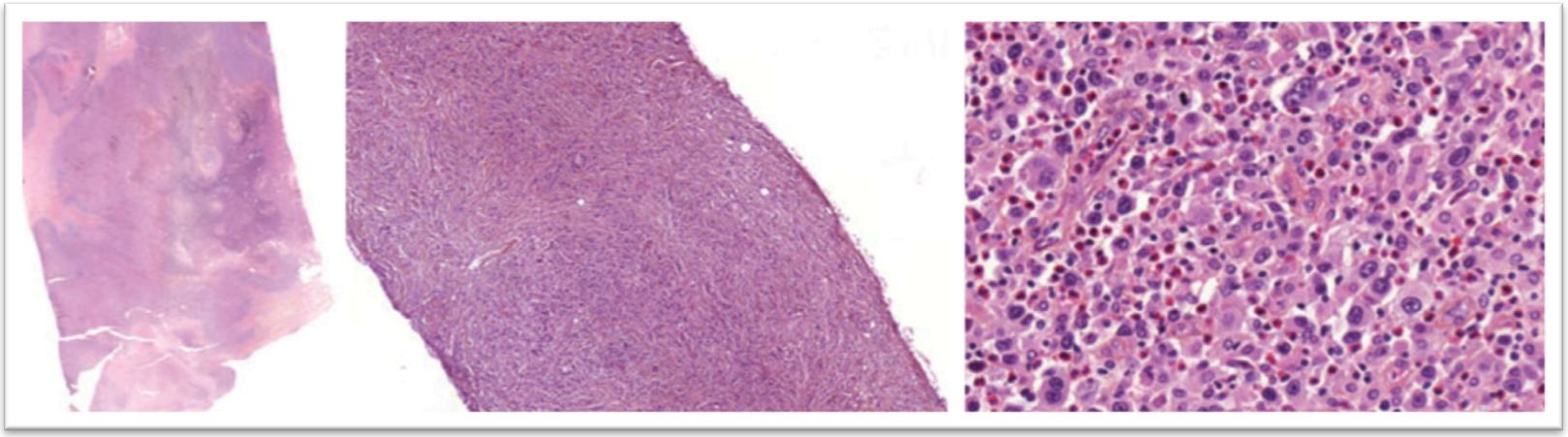
Anaplastic cell proliferation confined to the fibrous capsule



Laurent et al. Ann Oncol 2016

Infiltrative implant-associated ALCL

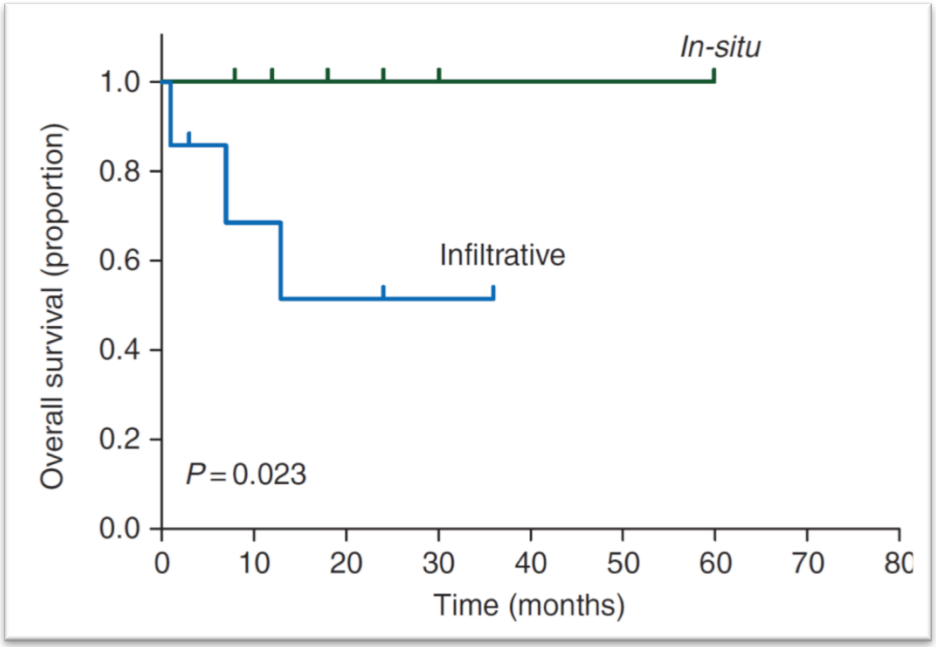
Pleomorphic cells massively infiltrating adjacent tissue with eosinophils and sometimes RS-like cells mimicking HL



Laurent et al. Ann Oncol 2016

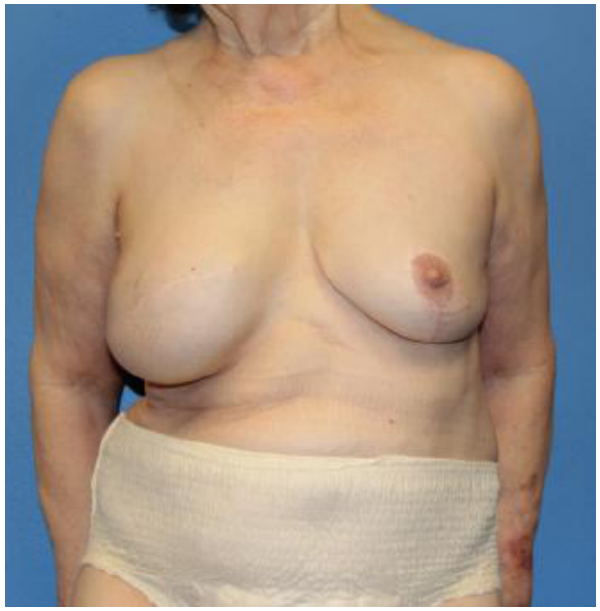
Breast implant-associated ALCL clinicopathological variants

- Effusion (seroma) → in situ ALK⁻ ALCL
- Tumor mass palpable → infiltrative ALK⁻ ALCL
- Seroma and mass

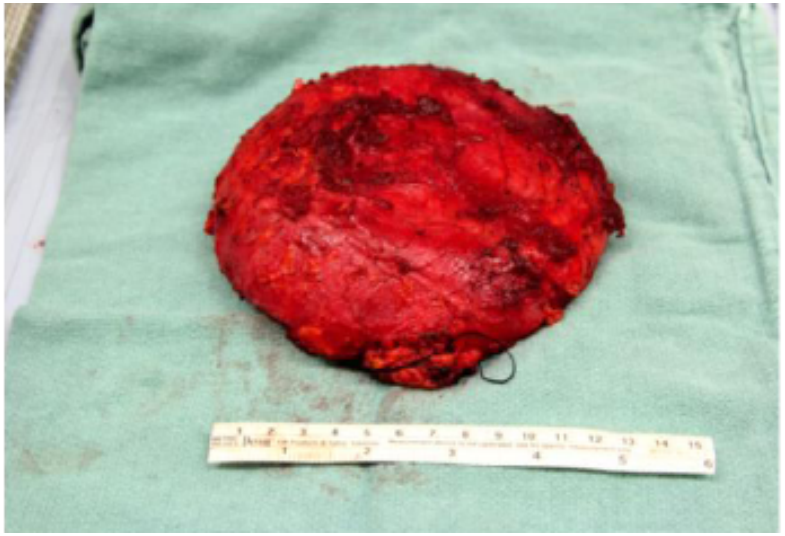


Laurent et al. Ann Oncol 2016

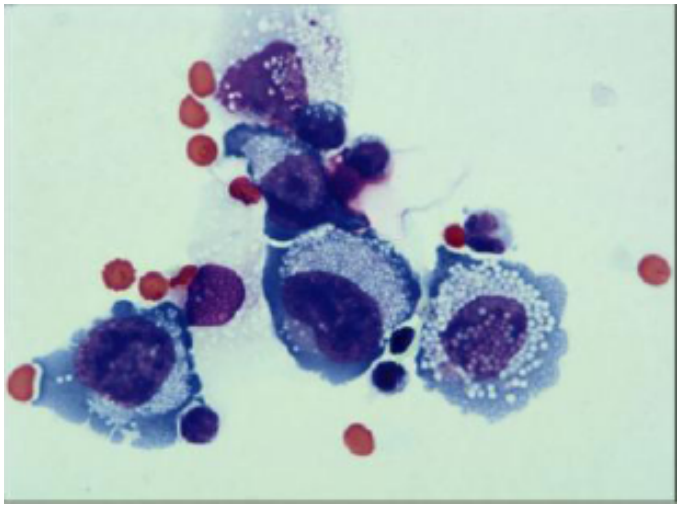
Large effusion of right breast



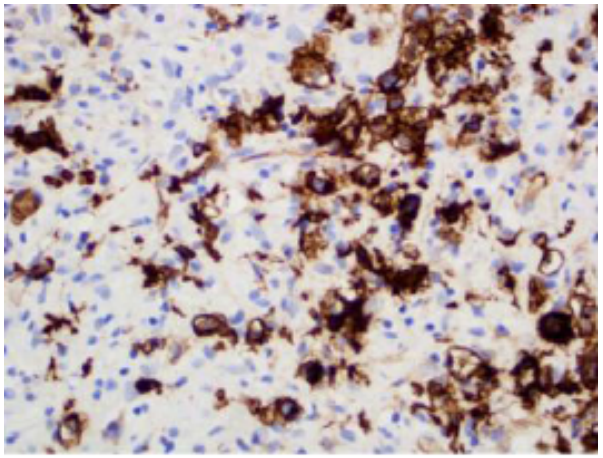
Capsulectomy with removal of an implant



Large cells with anaplastic morphology



IHC: staining for CD30



VOLUME 32 · NUMBER 2 · JANUARY 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Breast Implant–Associated Anaplastic Large-Cell Lymphoma: Long-Term Follow-Up of 60 Patients

A B S T R A C T

Purpose
Breast implant–associated anaplastic large-cell lymphoma (ALCL) is a recently described clinicopathologic entity that usually presents as an effusion-associated fibrous capsule surrounding an implant. Less frequently, it presents as a mass. The natural history of this disease and long-term outcomes are unknown.

Patients and Methods
We reviewed the literature for all published cases of breast implant–associated ALCL from 1997 to December 2012 and contacted corresponding authors to update clinical follow-up.

Results
The median overall survival (OS) for 60 patients was 12 years (median follow-up, 2 years; range, 0-14 years). Capsulectomy and implant removal was performed on 56 of 60 patients (93%). Therapeutic data were available for 55 patients: 39 patients (78%) received systemic chemotherapy, and of the 16 patients (28%) who did not receive chemotherapy, 12 patients opted for watchful waiting and four patients received radiation therapy alone. Thirty-nine (93%) of 42 patients with disease confined by the fibrous capsule achieved complete remission, compared with complete remission in 13 (72%) of 18 patients with a tumor mass. Patients with a breast mass had worse OS and progression-free survival (PFS; $P = .052$ and $P = .03$, respectively). The OS or PFS were similar between patients who received and did not receive chemotherapy ($P = .44$ and $P = .28$, respectively).

Conclusion
Most patients with breast implant–associated ALCL who had disease confined within the fibrous capsule achieved complete remission. Proper management for these patients may be limited to capsulectomy and implant removal. Patients who present with a mass have a more aggressive clinical course that may be fatal, justifying cytotoxic chemotherapy in addition to removal of implants.

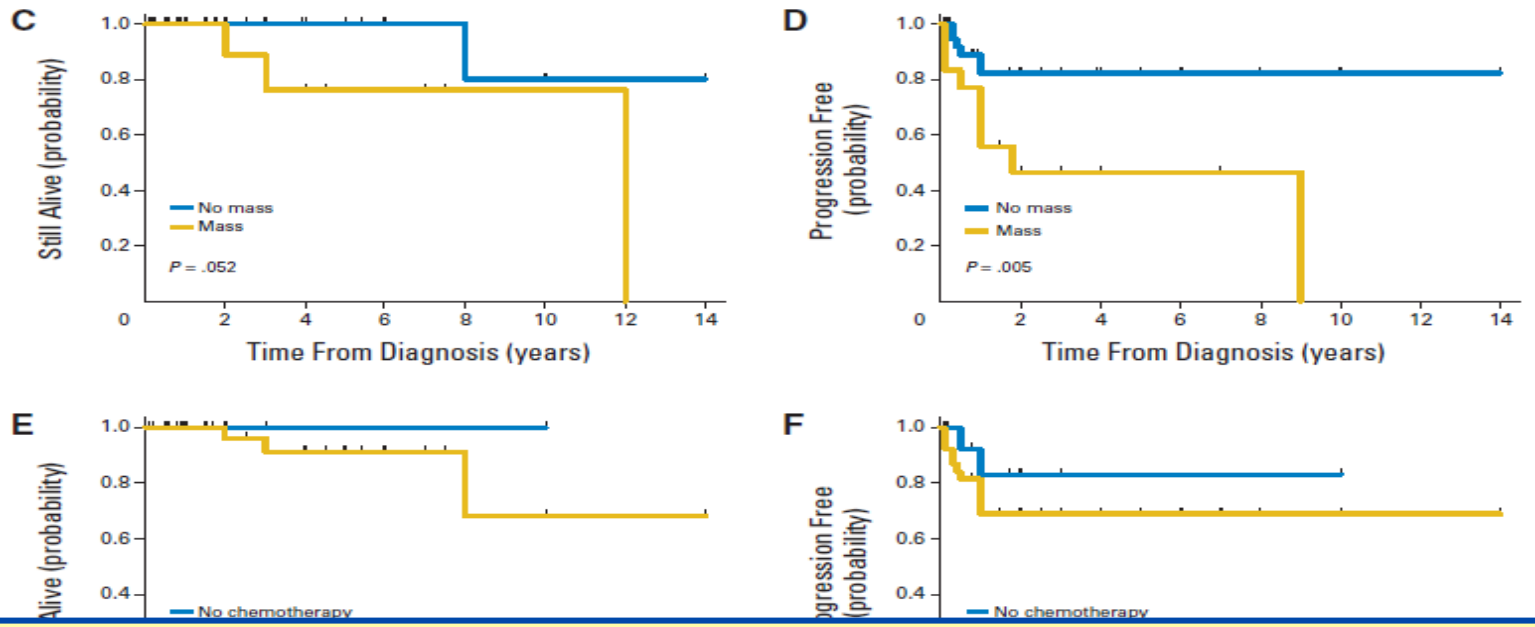
Miranda R et al. J.Clin. Oncol 2014

VOLUME 32 · NUMBER 2 · JANUARY 10 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

- 60 patients evaluated
- 56/60 (93%) patients performed capsulectomy;
- 55 pts evaluable: 39 CHT ; 16 no CHT : 12 watchful waiting and 4 IFRT
- 39/42 (93%) CR in patients with lymphoma confined by fibrous capsula
- 13/18 (72%) CR in patients with tumor mass



For patients with disease confined within fibrous capsule the optimal therapy should be limited to capsulectomy and implant removal

Miranda R et al. J.Clin. Oncol 2014

VOLUME 34 · NUMBER 2 · JANUARY 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

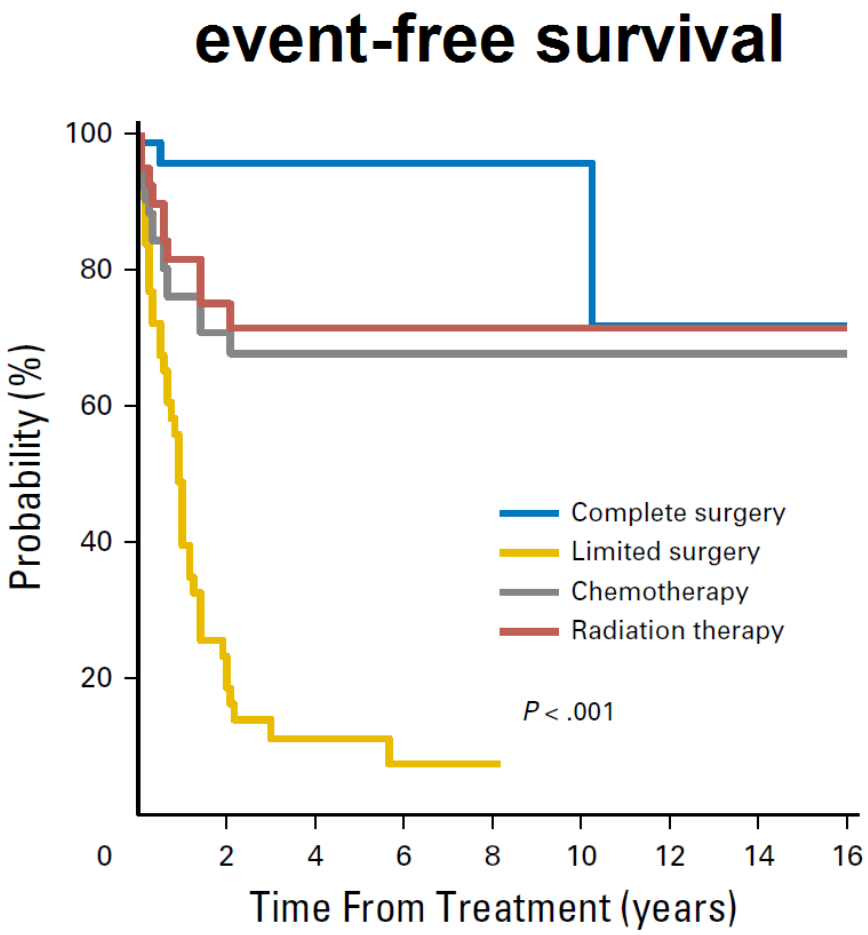
Complete Surgical Excision Is Essential for the Management of Patients With Breast Implant–Associated Anaplastic Large-Cell Lymphoma

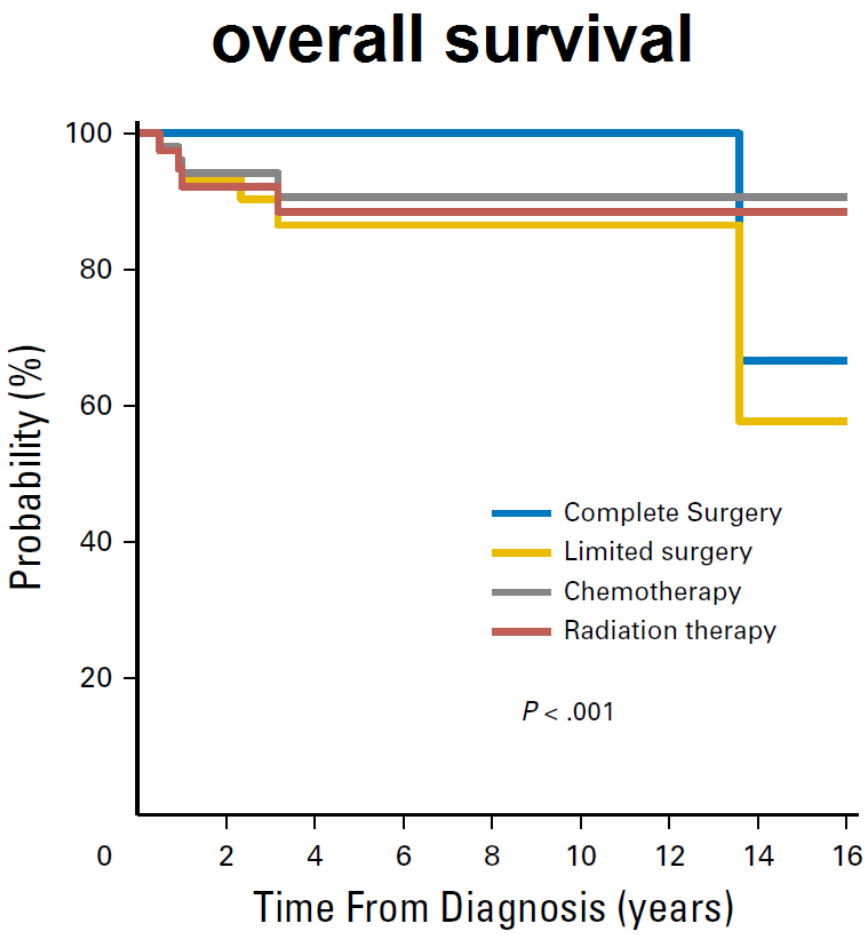
Mark W. Clemens, L. Jeffrey Medeiros, Charles E. Butler, Kelly K. Hunt, Michelle A. Fanale, Steven Horwitz, Dennis D. Weisenburger, Jun Liu, Elizabeth A. Morgan, Rashmi Kanagal-Shamanna, Vinita Parkash, Jing Ning, Aliyah R. Sohani, Judith A. Ferry, Neha Mehta-Shah, Ahmed Dogan, Hui Liu, Nora Thormann, Arianna Di Napoli, Stephen Lade, Jorge Piccolini, Ruben Reyes, Travis Williams, Colleen M. McCarthy, Summer E. Hanson, Loretta J. Nastoupil, Rakesh Gaur, Yasuhiro Oki, Ken H. Young, and Roberto N. Miranda

81 patients

Clinical Feature	Patients With BI-ALCL
Age, years	
Median	54
Range	28-87
Laterality	
Right	46 (52.9)
Left	37 (42.5)
Bilateral	4 (4.6)
Reason for initial implantation	
Cosmetic	51 (58.6)
Breast cancer reconstruction	36 (41.4)
Type of implant (n = 81)	
Silicone	40 (49.4)
Saline	41 (50.6)
Texture of implant (n = 48)	
Purely textured	45 (93.7)
Purely smooth	0 (0)
Both smooth/textured	3 (2.3)
Interval to lymphoma diagnosis, years	
Median	8
Mean	9.1
Range	2-25
Clinical presentation	
Effusion only	52 (59.8)
Mass only	15 (17.2)
Effusion and mass	17 (19.5)
No mass, no effusion	3 (3.4)
TNM stage at presentation	
IA	31 (35.6)
IB	10 (11.5)
IC	12 (13.8)
IIA	22 (25.3)
IIB	4 (4.6)
III	8 (9.2)
IV	0 (0)
Chemotherapy (n = 51)	
CHOP	44 (86.3)
3 cycles	11
4 cycles	2
6 cycles	28
NA	3
CHOEP	11 (21.6)
6 cycles	11
NS	2 (3.9)
ABVD	2 (3.9)
Hyper-CVAD	1 (1.9)
Follow-up, months	
Median	30
Mean	45
Range	3-217

Complete surgical excision essential in breast implant-associated ALCL





Clemens et al. J Clin Oncol 2016

Proposed TNM staging for Breast implant-associated ALCL

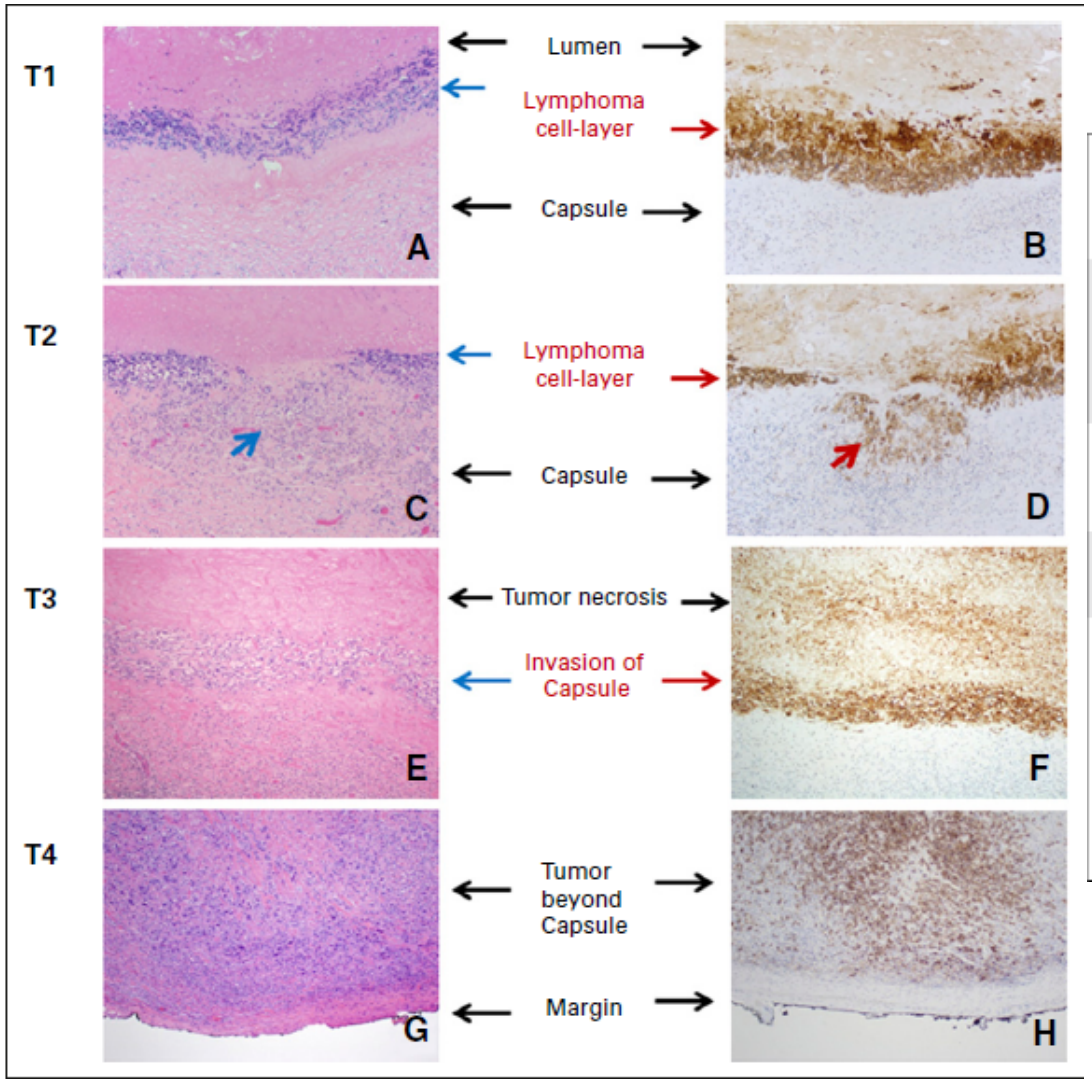
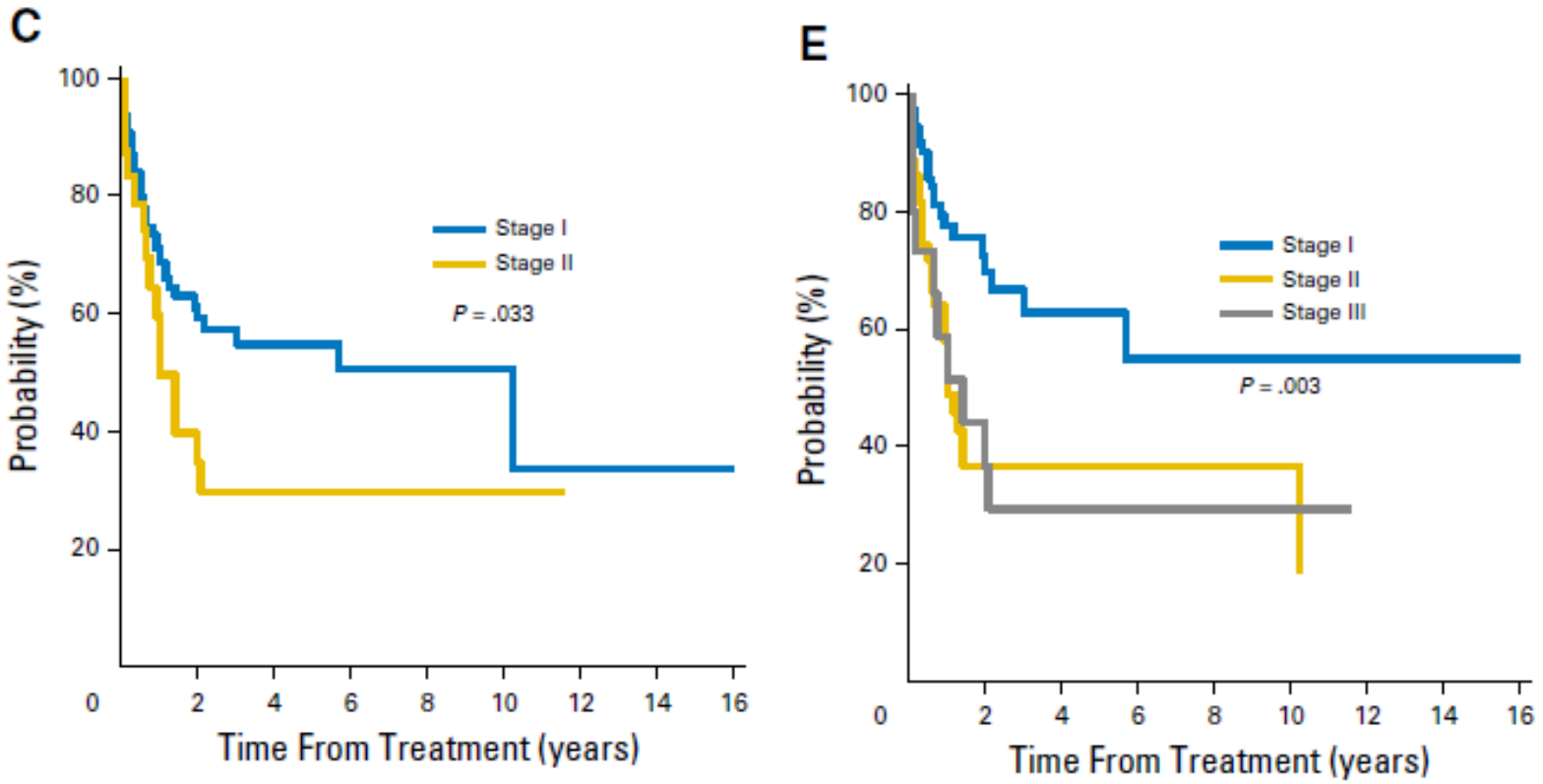


Table 1. Proposed TNM Staging for Breast Implant–Associated Anaplastic Large-Cell Lymphoma

TNM or Stage Designation	Description	
T: tumor extent		
T1	Confined to effusion or a layer on luminal side of capsule	
T2	Early capsule infiltration	
T3	Cell aggregates or sheets infiltrating the capsule	
T4	Lymphoma infiltrates beyond the capsule	
N: lymph node		
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/distant sites	
Stage		
IA	T1N0M0	Stage 1
IB	T2N0M0	
IC	T3N0M0	
IIA	T4N0M0	Stage 2
IIB	T1-3N1M0	
III	T4N1-2M0	
IV	TanyNanyM1	

Clemens et al. J Clin Oncol 2016

Proposed TNM staging for Breast implant-associated ALCL



Patients with lymphoma confined by the fibrous capsule surrounding the implant have better EFS and OS than those with lymphoma that had spread beyond the capsule (P = .03)

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Management of suspected and confirmed BIA-ALCL

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