

Les Lymphomes de la Zone marginale

Une définition « anatomique »

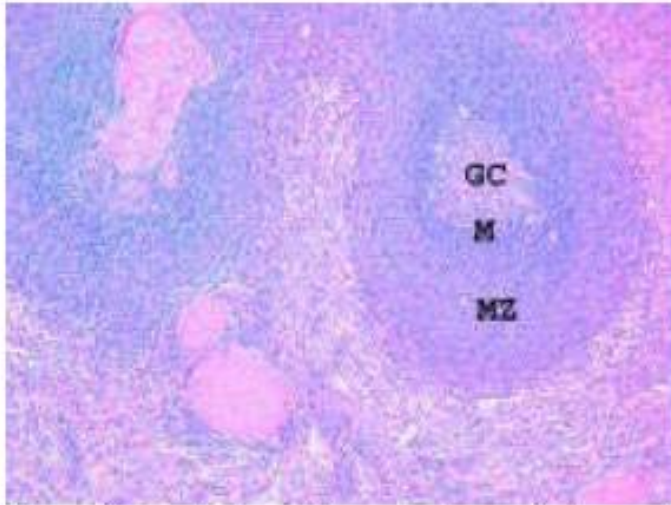


Figure 1. Normal spleen, white pulp; the germinal centers (GC) are surrounded by a lymphocytic corona of mantle cells (M) and a marginal zone area (MZ) (hematoxylin-eosin).

Rate

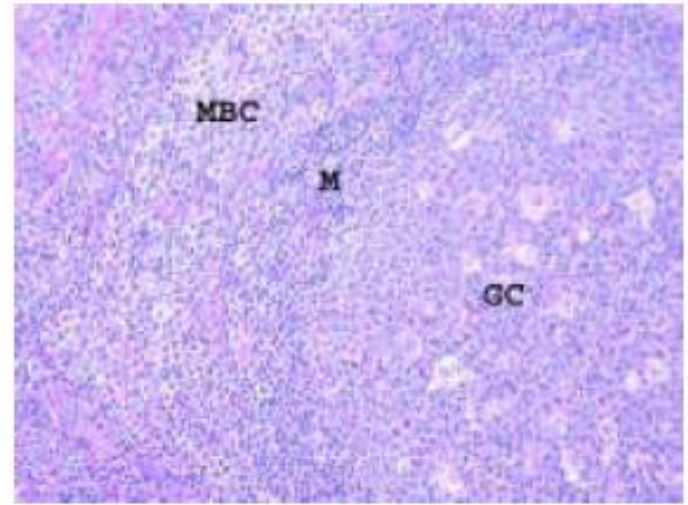


Figure 3. Toxoplasmic lymphadenitis; an expanded marginal zone area composed of monocytyoid B-cells (MBC) surrounds the lymphoid follicle (hematoxylin-eosin).

Intestin

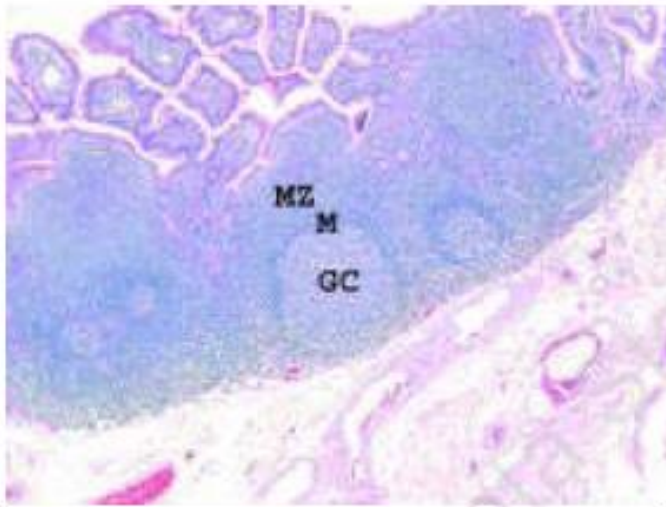


Figure 2. Small bowel; the lymphoid Peyer's patches consist of GC surrounded by M and MZ, prominent at the mucosal side (hematoxylin-eosin).

Ganglion

Trois définitions « pathologiques »

- Lymphome de la zone marginale des tissus lymphoïdes associés aux muqueuses: MALT
- Lymphome de la zone marginale spléniques
- Lymphomes de la zone marginale ganglionnaires

Définition immunophénotypique et cytogénétique

Lymphoma type	CD5	CD10	CD23	CD43	Cytogenetic abnormality
Marginal zone/MALT lymphoma	-	-	-	-/+	t(11;18) t(1;14) t(14;18) (q32;q21) t(3;14) Tri- somy 3, 18
SLL	+	-	+	+	Del 13q14 Trisomy 12
Follicular	-	+/-	-/+	-	t(14;18)
Mantle	+	-/+	-	+	t(11;14)

Physiopathologie

Stimulation antigénique chronique:
Antigènes autologues ou microbiens

MALT et maladies auto immunes
Hashimoto
Sjögren
Pneumopathie interstitielle lymphoïde

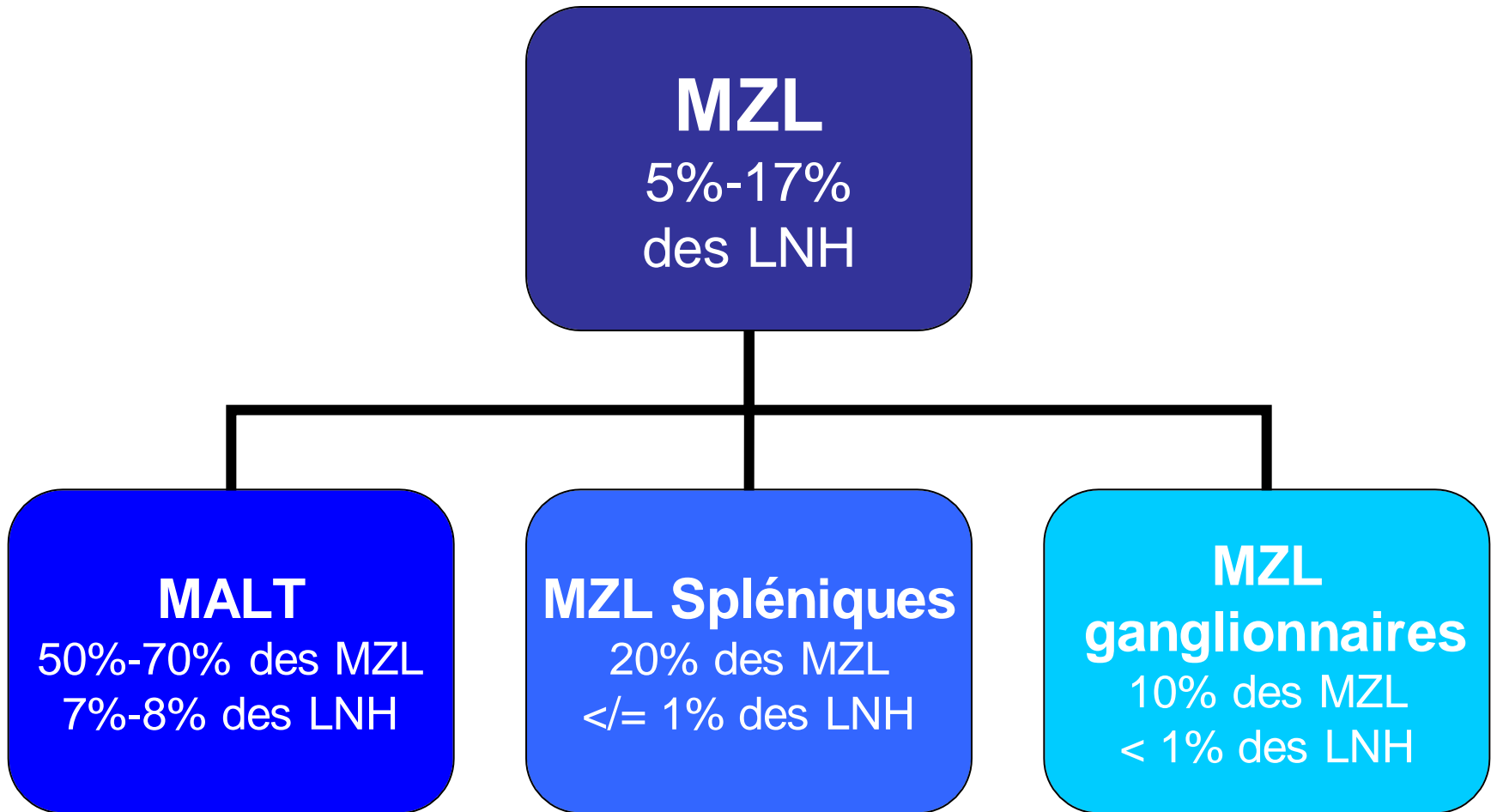
Hépatite C et
MALT
MZL splénique
MZL ganglionnaire

MALT et stimulation microbienne
Helicobacter Pylori: Gastrique
Borrelia Burgdorferi: Cutané
Chlamydia Psittaci: Annexes de l'oeil
Campylobacter Jejuni: Intestin grêle

Définition immunophénotypique et cytogénétique

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SLL	+	-	+	+	Del 13q14 Trisomy 12
Follicular	-	+/-	-/+	-	t(14;18)
Mantle	+	-/+	-	+	t(11;14)

Épidémiologie

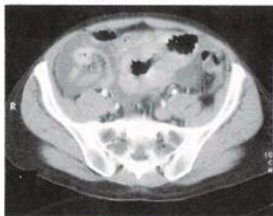


Les différentes présentations des lymphomes de la zone marginale

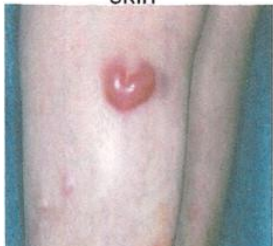
MALT lymphoma

Extranodal locations

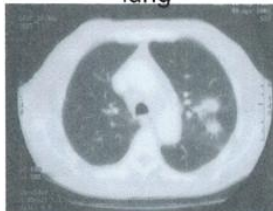
intestine



skin



lung



thyroid



Splenic MZL

Massive splenomegaly



MZL

Variety of clinical presentations

B symptoms

- weight loss
- fever
- fatigue

Disseminated nodal involvement

Peripheral:

- neck predominant

Central:

- paraaortic predominant

Nodal MZL

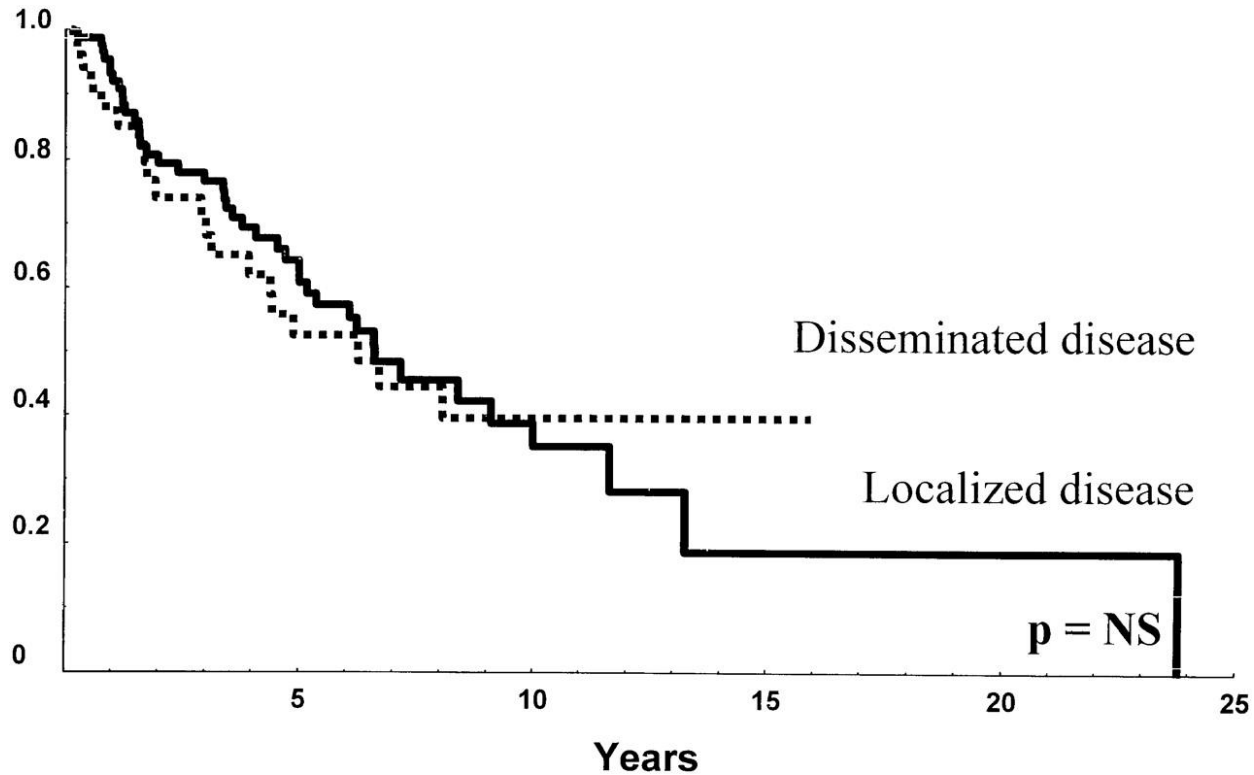


Caractéristiques communes

- Bon PS
- Pas de signes « B »
- LDH et Beta 2 microglobuline Normaux
- Localisés dans 60% à 70% des cas
- Disséminé dans 30% des cas*
 - Multiples sites muqueux: 30%
 - Moelle osseuse: 44%
 - Ganglions multiples: 22%
 - Site extra ganglionnaire extramuqueux: 4%

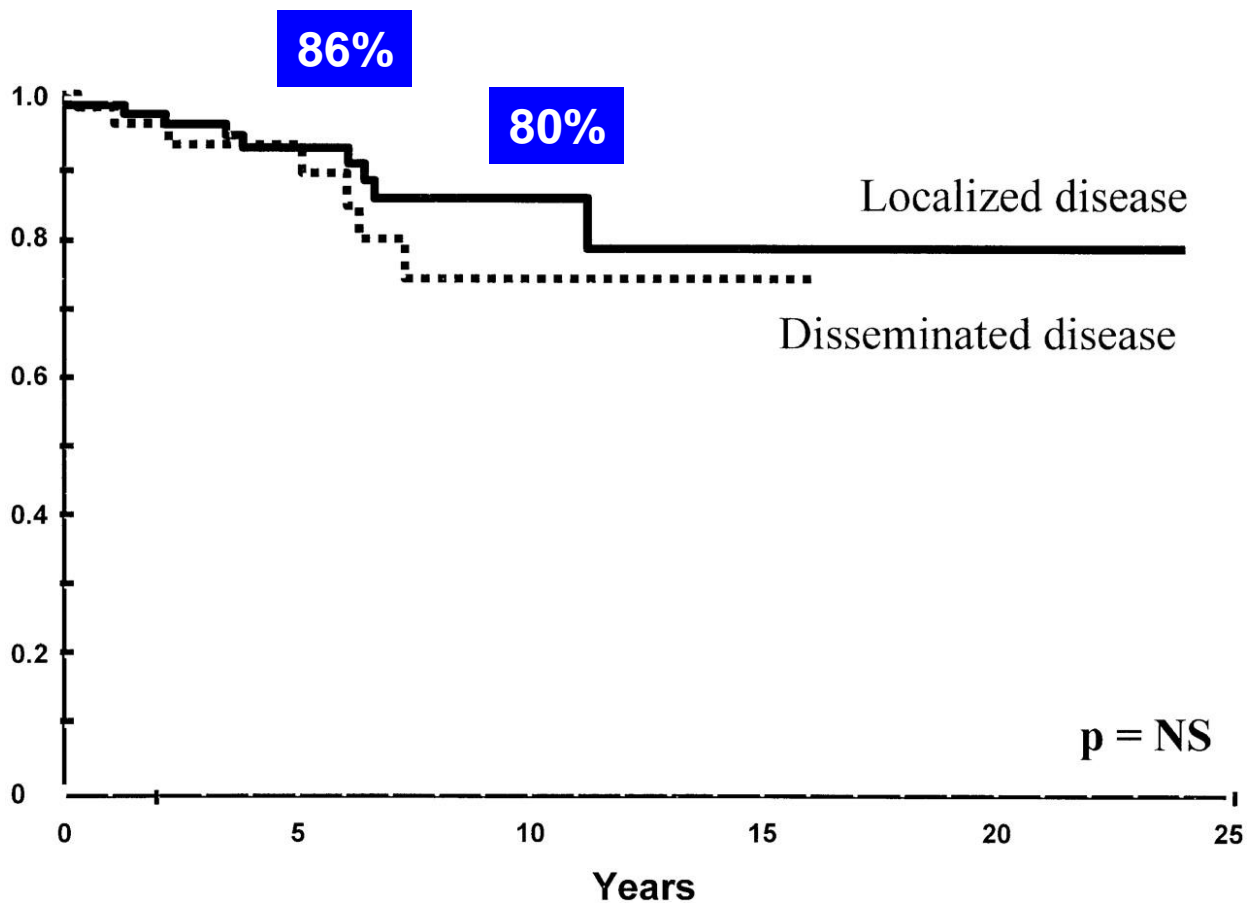
***: Thieblemont C et al. Blood 2000;95:802**

Survie sans progression Mediane: 5 ans et demi



Thieblemont, C. et al. Blood 2000;95:802-806

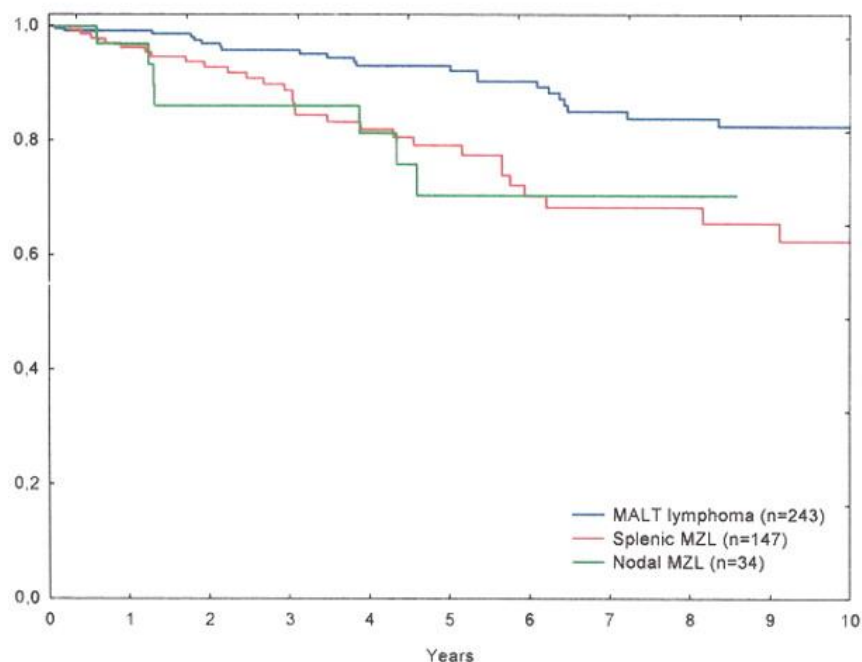
Survie globale: Suivi median: 4 ans



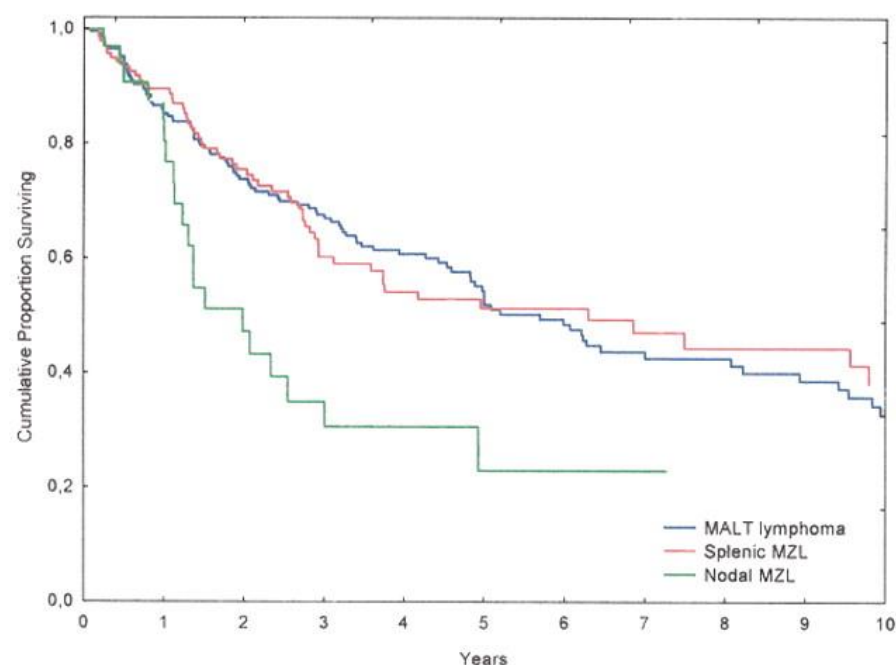
Thieblemont, C. et al. Blood 2000;95:802-806

Survie globale et survie sans progression pour 424 patients porteurs de lymphomes de la zone marginale traités entre 1988 et 2005 à Lyon (Thieblemont C)

Overall survival



FFP survival



Hematology 2005;2005:544-552

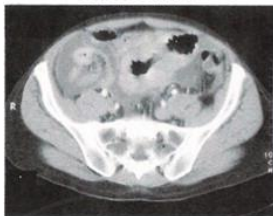
Lymphomes spléniques à lymphocytes villeux (SLVL)

Les différentes présentations des lymphomes de la zone marginale

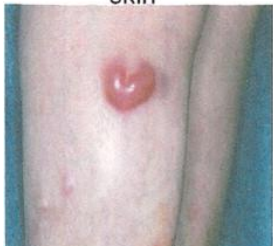
MALT lymphoma

Extranodal locations

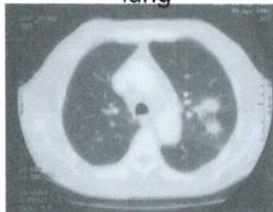
intestine



skin



lung



thyroid



Splenic MZL

Massive splenomegaly



MZL

Variety of clinical presentations

B symptoms

- weight loss
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- fatigue

Disseminated nodal involvement

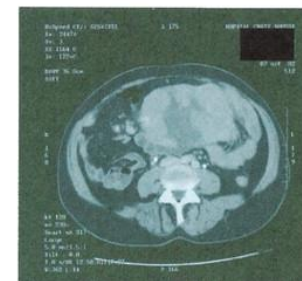
Peripheral:

- neck predominant

Central:

- paraaortic predominant

Nodal MZL



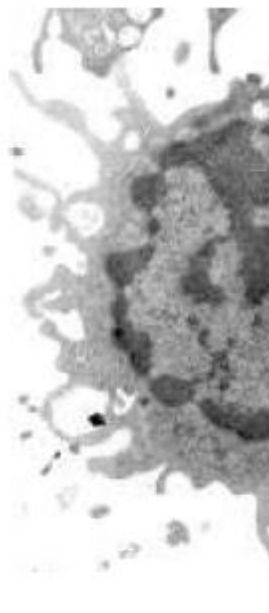


Figure 4. Electron microscopically plastic circulating lymphocyte projections.

Table 3. Prognostic factors in splenic marginal zone B-cell lymphoma with or without villous lymphocytes.

<i>Reference</i>	<i>Adverse prognostic factors</i>
Troussard <i>et al.</i> ⁶⁰ (SLVL)	Leukocytes > 30×10 ⁹ /L Lymphocytes < 4×10 ⁹ /L Chemotherapy
Thieblemont <i>et al.</i> ⁶¹ (SMZL/SLVL)	Monoclonal component β2-microglobulin level Leukocytes > 20×10 ⁹ /L Lymphocytes > 9×10 ⁹ /L
Chacón <i>et al.</i> ⁶² (SMZL)	ECOG performance status ≥ 2 Incomplete response Non-hematopoietic site involvement
Baldini <i>et al.</i> ⁸⁵ (SMZL) Gruszka-Westwood <i>et al.</i> ⁸⁶ (SLVL) Chacón <i>et al.</i> ⁶² (SMZL)	p53 alteration
Algara <i>et al.</i> ⁸⁷ (SMZL)	IgV _H unmutated + 7q deletion

SMZL: splenic marginal zone B-cell lymphoma; SLVL: splenic lymphoma with villous lymphocytes.

SMZL: splenic marginal zone B-cell lymphoma; SLVL: splenic lymphoma with villous lymphocytes.

Lymphome de la zone marginale splénique

Splenectomie

Si contre-indiquée:

- **Rituximab:** 375 mg/m²/sem x 4
- **Chloraminophene:** 16 mg/m²/j x 5j/m x 6m ou 6 mg/m²/j x 6m
- **Cyclophosphamide:** 10 mg/m²/j x 6-12 m
- **Fludarabine:** 30 mg/m²:m x 6 m

Si associé à HCV

pegIFN- α 2b (1.0 μ g/kg/sem)
+ ribavirine (1000-1200 mg/j)

Facteurs de mauvais pronostic: LDH, Signes B ou 20% à 50% de **grandes cellules** sur la splénectomie ou **Ganglions intraabdominaux** + lors de la laparotomie:

- **R-CHOP 21 x 6**
- **R-FC 28 x 6**

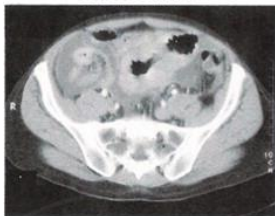
Les Lymphomes de type MALT

Les différentes présentations des lymphomes de la zone marginale

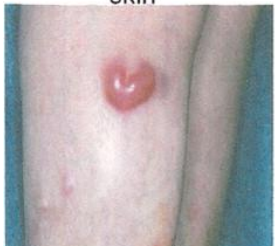
MALT lymphoma

Extranodal locations

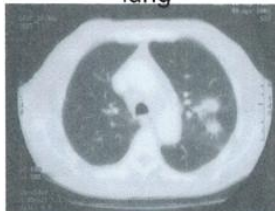
intestine



skin



lung



thyroid



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Massive splenomegaly



MZL

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Disseminated nodal involvement

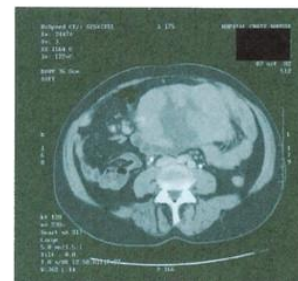
Peripheral:

- neck predominant

Central:

- paraaortic predominant

Nodal MZL



	Gastrointestinal Tract Location		Non-gastrointestinal Tract Location					
	Stomach	Intestine	Lung	Thyroid	Head and Neck (Salivary glands)	Skin	Orbit	Breast
Age, median, years	56	59	60	60	63	55	63	55
Male: female ratio	1:1.7	1.2:1	1:1.7	0:10	1:4.5	1.1:1	1:2	1:1.5
Localized disease	87%	45%	62%	83%	73%	59%	67%	40%
Bone marrow involvement	13%	35%	38%	17%	18%	29%	10%-22%	20%
Symptoms at presentation								
B symptoms								
Weight loss	15%-32%	50%	10%-19%	0-7%	7%	—		0%
Fever and night sweat	3.5%, range 1%–9%	—	—	0-7%	7%	24%		0%
Specific to location	Epigastric pain 53-81%	Abdominal pain	Asymptomatic 56%	Thyroid 100%	Asymptomatic 95%	Nodule	Orbital mass	Breast mass
	Dyspepsia 32-34%	Occlusion	Cough 17%	Mass 9-23%	Mass 5%	Erythema	Bulging eye	Breast pain
	Vomiting 8-31%	Perforation	Dyspnea 15%	Hoarseness 30%	Auditory trouble	Pruritus	Diplopia	
	Gastric bleeding 2-33%		Hemoptysis 7%	Dysphagia 30%				
	Anemia (Hb < 12g/L) 30%		Chest pain 2%	Dyspnea				

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Anemia (Hb < 12g/L)	30%		Chest pain 2%

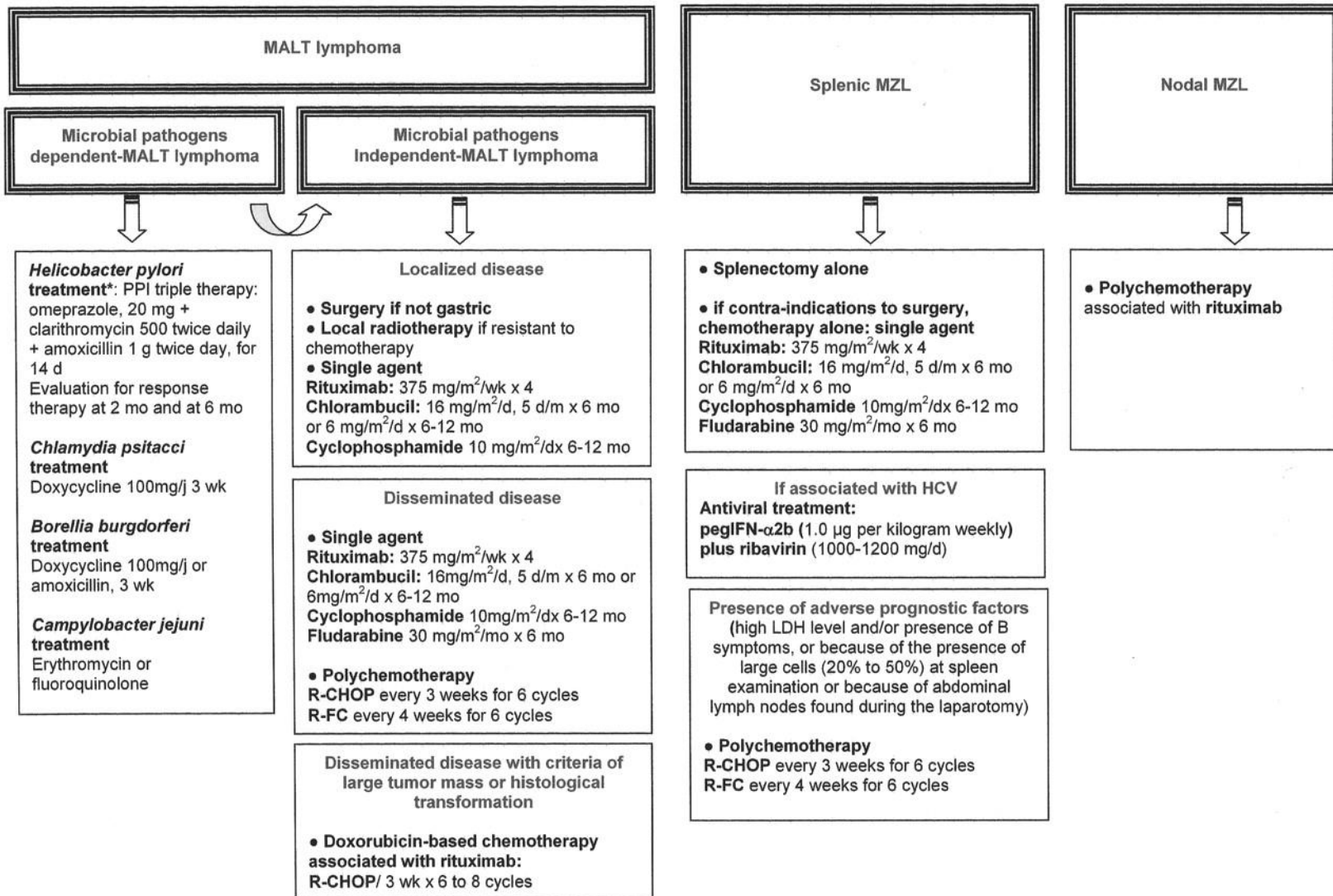
Non-gastrointestinal Tract Location

Thyroid		Head and Neck (Salivary glands)		Skin	Orbit	Breast
60		63		55	63	55
0:10		1:4.5		1.1:1	1:2	1:1.5
83%		73%		59%	67%	40%
17%		18%		29%	10%-22%	20%
0-7%		7%		—		0%
0-7%		7%		24%		0%
Thyroid Mass	100%	Asymptomatic Mass	95%	Nodule	Orbital mass	Breast mass
Hoarseness	9-23%	Auditory trouble	5%	Erythema	Bulging eye	Breast pain
Dysphagia	30%			Pruritus	Diplopia	
Dyspnea	30%					

Bilan d'extension

- Bilan d'extension ultra précis utile?
- Essayer de documenter l'implication microbienne par des techniques de PCR.
- Sur des prélèvements effectués « in-situ »

Options thérapeutiques pour les Lymphomes de la zone marginale



Lymphomes du MALT dépendant d'un agent microbien

Helicobacter Pylori:

Traitement:

Omeprazole 20 mg + clarithromycine 500 x 2/j +

Amoxicilline 1g x 2/j x 14 jours

Evaluation de la réponse à 2 mois et à 6 mois

Chlamydia psitacci:

Traitement: Doxycycline 100 mg/j x 3 semaines

Borellia burdorferi:

Traitement: Doxycycline 100 mg/j ou amoxicilline x 3 sem

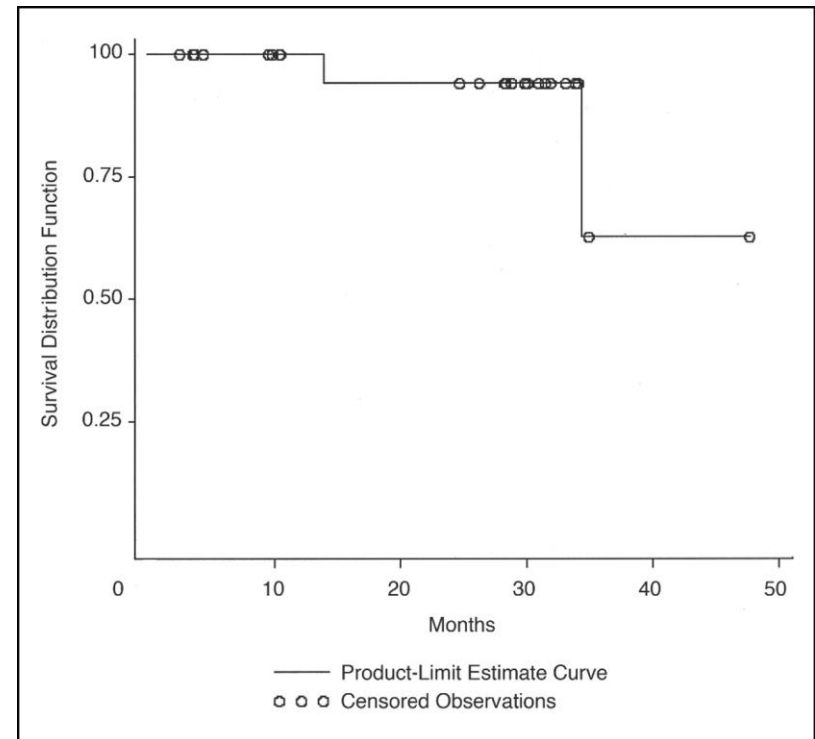
Campylobacter jejuni:

Traitement: Erythromycine ou fluoroquinolone

Rituximab pour MALT gastrique

	Patients	
	N	%
Réponse complète	12	46
Réponse partielle	8	31
Maladie stable	6	23

Réponse au traitement



Time to treatment failure (progression or death)

Martinelli, G. et al. J Clin Oncol; 23:1979-1983 2005

Maladie Localisée

- **Chirurgie** sauf gastrique
- **Radiothérapie locale**
- **Rituximab**: 375 mg/m²/sem x 4
- **Chloraminophene**: 16 mg/m²/j x 5j/m x 6m ou 6 mg/m²/j x 6-12m
- **Cyclophosphamide**: 10 mg/m²/j x 6-12m

Maladie disséminée

Mono thérapie

- **Rituximab**: 375 mg/m²/sem x 4
- **Chloraminophene**: 16 mg/m²/j x 5j/m x 6m ou 6 mg/m²/j x 6-12m
- **Cyclophosphamide**: 10 mg/m²/j x 6-12m
- **Fludarabine**: 30 mg/m²/m x 6m

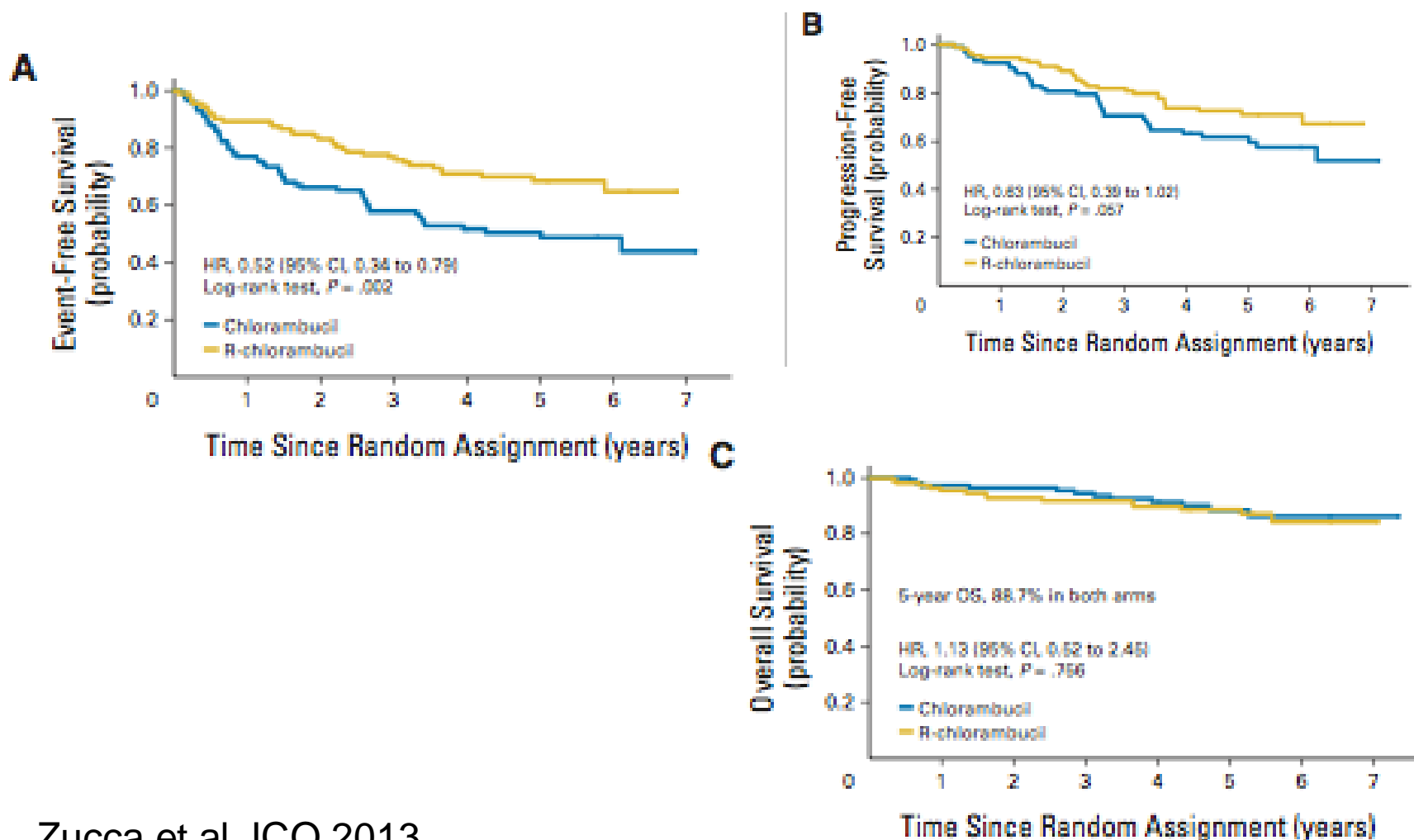
Polychimiothérapie

- **R-CHOP 21 x 6**
- **R-FC 28 x 6**

Maladie disséminée de forte masse tumorale ou transformée

- **R-CHOP 21 x 6-8**

Addition of Rituximab to Chlorambucil Produces Superior Event-Free Survival in the Treatment of Patients With Extranodal Marginal-Zone B-Cell Lymphoma: 5-Year Analysis of the IELSG-19 Randomized Study



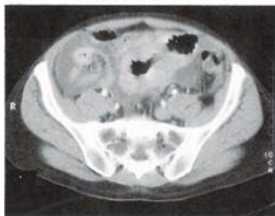
Lymphome de la zone marginale ganglionnaire

Les différentes présentations des lymphomes de la zone marginale

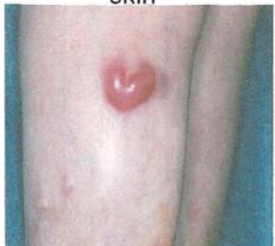
MALT lymphoma

Extranodal locations

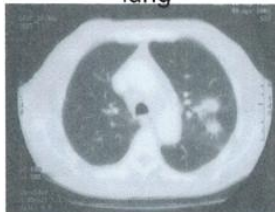
intestine



skin



lung

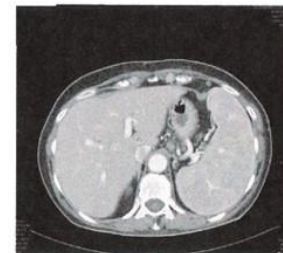


thyroid



Splenic MZL

Massive splenomegaly



MZL Variety of clinical presentations

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- weight loss
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- fatigue

Disseminated nodal involvement

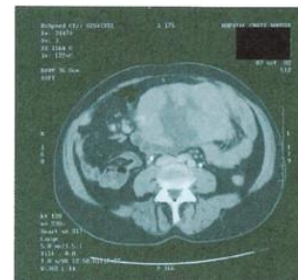
Peripheral:

- neck predominant

Central:

- paraaortic predominant

Nodal MZL



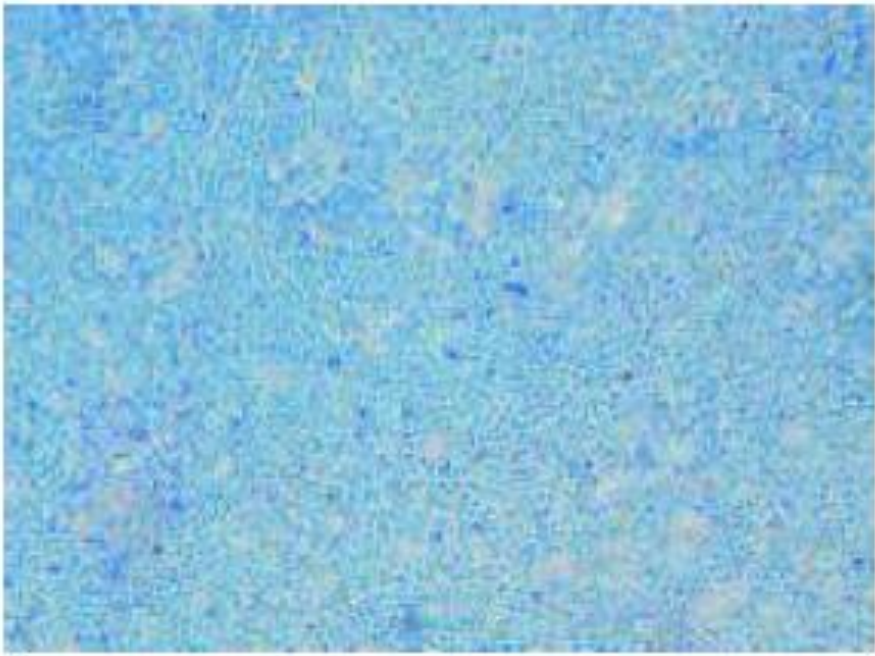


Figure 8. Nodal MBCL: lymphoma cells surround and partially colonize the germinal center (Giemsa).

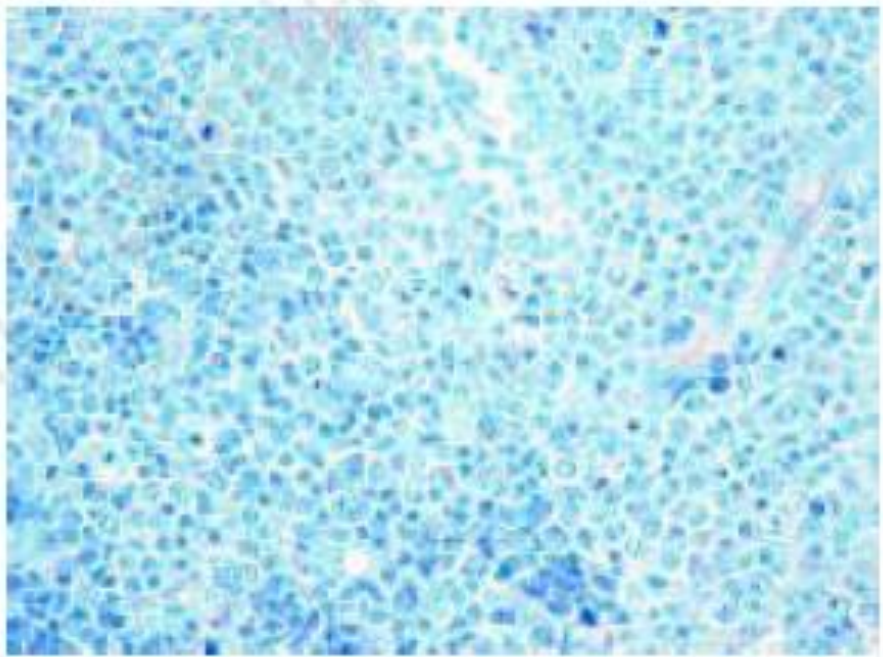


Figure 9. Nodal MBCL (the same case pictured in Figure 8): higher magnification detailing the cytologic features of the lymphoma population, including cells medium in size with a quite irregular nucleus and a fairly broad rim of gray cytoplasm, scattered larger *blast* cells, and elements with features of plasma cell differentiation.

Lymphome de la zone marginale ganglionnaire

Polychimiothérapie et Rituximab

Ou

Bendamustine et Rituximab

Conclusion (I)

- Des lymphomes en règle générale peu évolutifs, souvent localisés, peu agressifs.
- Un bilan d'extension adapté, qui peut être « minimal »
- Un traitement « doux » avec des agents anti infectieux avant de se précipiter sur la chimiothérapie ou la radiothérapie.
- La chirurgie est exceptionnellement nécessaire et toujours délabrante!

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Marginal zone-related neoplasms of splenic and nodal origin

LUCA ARCAINI, MARCO PAULLI, EMANUELA BOVERI, UMBERTO MAGRINI, MARIO LAZZARINO

Haematologica 2003;88:80-93



Clinical Presentation and Management of Marginal Zone Lymphomas

Catherine Thieblemont
Hematology 2005

The
Oncologist[®]

Lymphoma

Non-Hodgkin's Lymphoma of Mucosa-Associated Lymphoid Tissue

SETH M. COHEN,^{a,c} MAGDALENA PETRYK,^{a,c} MALA VARMA,^{a,c} PETER S. KOZUCH,^{a-c}
ELIZABETH D. AMES,^a MICHAEL L. GROSSBARD^{a-c}