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ESMO Clinical Practice Guidelines

Gastric Marginal Zone Lymphoma of MALT

Discussion

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Disclosures

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Gastric MALT Lymphoma

Extranodal marginal zone B-cell lymphoma

- Most common MALT lymphoma
- Pathogenetic link with H. pylori
- Recent attempts to overcome controversies on its management:
  - EGILS Consensus Report on gastric MALT lymphoma *(Ruskone Formestraux et al. Gut 2011)*
  - ESMO Guidelines Consensus Conference *(Dreyling et al. Ann Oncol 2012)*
  - **ESMO Guidelines for Gastric MALT lymphoma *(Zucca et al. Ann Oncol 2014)***

Staging of gastric MALT Lymphoma

- H. Pylori status (by immunohistochemistry and serology)
- History and physical exam
- Esophagogastroduodenoscopy with multiple biopsies
- Endoscopic ultrasound to evaluate the regional lymph nodes and gastric wall infiltration
- Complete blood counts and basic biochemistry
- HIV, HBV and HCV serologies
- CT scan of the chest, abdomen and pelvis
- Bone marrow aspirate and biopsy
- PET use is controversial and has uncertain clinical utility

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Most gastric MALT lymphomas regress after *H. pylori* eradication

Reference	n	Staging procedure	CR rate (%)	Time to CR (mo.)	Relapses (n)
Savio, 1996	12	CT+EGD	84	2-4	0
Pinotti, 1997	45	CT+EGD	67	3-18	2
Neubauer, 1997	50	CT±EUS	80	1-9	5
Nobre Leitao, 1998	17	CT+EUS	100	1-12	1
Steinbach, 1999	23	CT±EUS	56	3-45	0
Montalban, 2001	19	CT±EUS	95	2-19	0
Ruskone-Formestraux, 2001	24	CT+EUS	79	2-18	2
Bertoni, 2002		CT+EGD	62	3-24	15
Zullo, 2010 (systematic review)	**1408**		**77.5**	**5 (median)**	**72/994**

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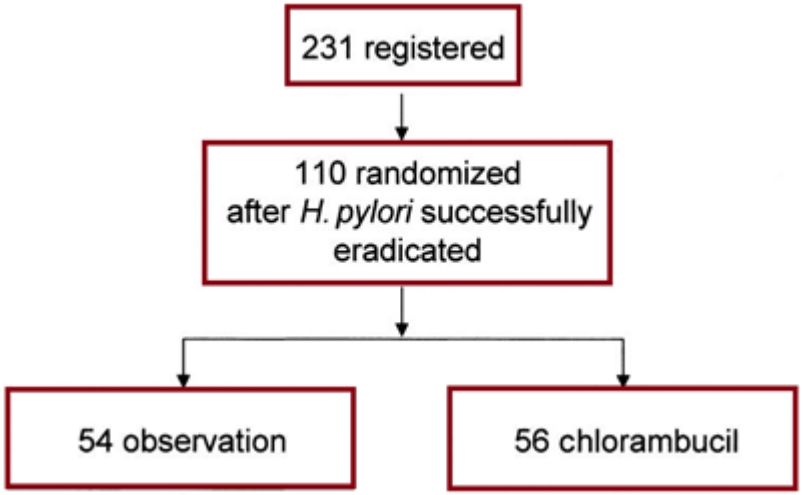
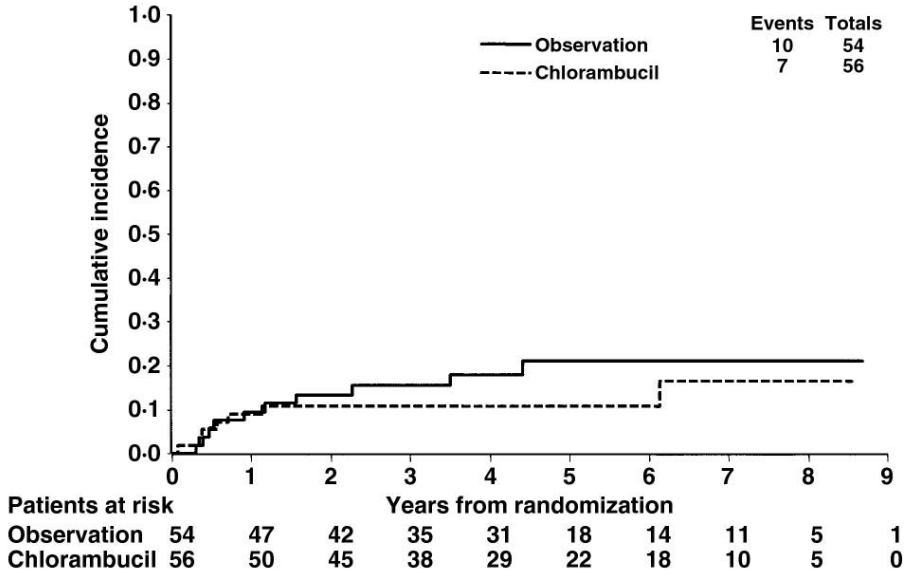
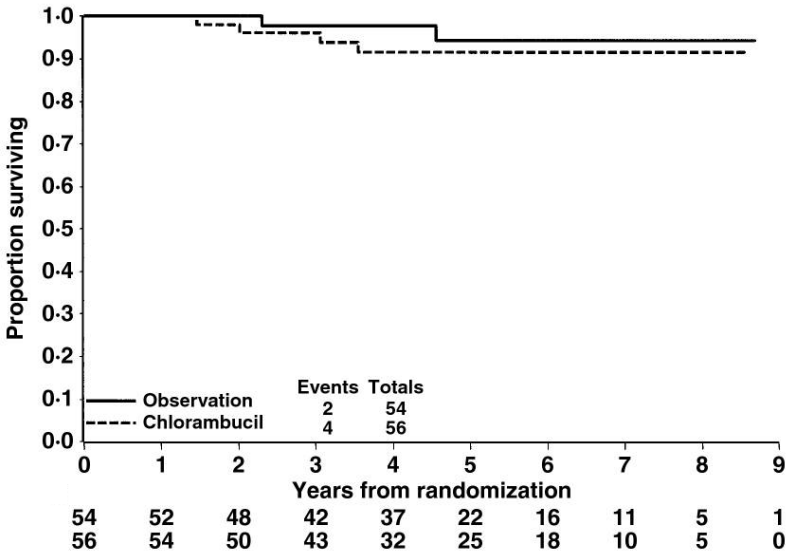
Chlorambucil versus observation after anti-*Helicobacter* therapy in gastric MALT lymphomas: Results of the international randomised LY03 trial.



Cumulative incidence rate of relapse/PD



Overall survival



Hancock et al. BJH 2009

Treatment of gastric MALT Lymphoma

HP eradication alone is the standard initial therapy for *HP*+ disease

Recommendations

- Helicobacter pylori eradication therapy must be given to all gastric MALT lymphomas, independently of stage
- Re-evaluation of H. pylori status by breath test ±EGDS at ~2-3 months after antibiotics, then EGD every 3-6 months to document the lymphoma regression
- wait for at least 12 months before starting another treatment (the time needed to obtain a remission can span from very few months to ~24 months)

Treatment of gastric MALT Lymphoma

***HP* eradication is the standard initial therapy for *HP*+ disease but some issues remain:**

- need of molecular studies
- antibiotics in H. pylori-negative cases?
- evaluation of responses
- treatment of residual disease
- follow up policies following antibiotics

Treatment of gastric MALT Lymphoma

Molecular studies

Demonstration of monoclonality by PCR analysis of the rearranged Ig genes is not a prerequisite for the diagnosis

Detection of **t (11;18)** may help distinguish:

- patients who are unlikely to respond to antibiotic therapy
- and unlikely to respond to alkylating agents alone

Treatment of gastric MALT Lymphoma

Antibiotics in H. pylori-negative cases?

Recommendation: In *H. pylori*-negative cases … the administration of an anti-*Helicobacter* regimen may be worthwhile…

- False negative diagnostic test
- Other microorganisms involved (*H. heilmannii*)
- Responses in 14 of 72 published cases (19%)

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The GELA Histologic Grading System is recommended for Post-Treatment Evaluation

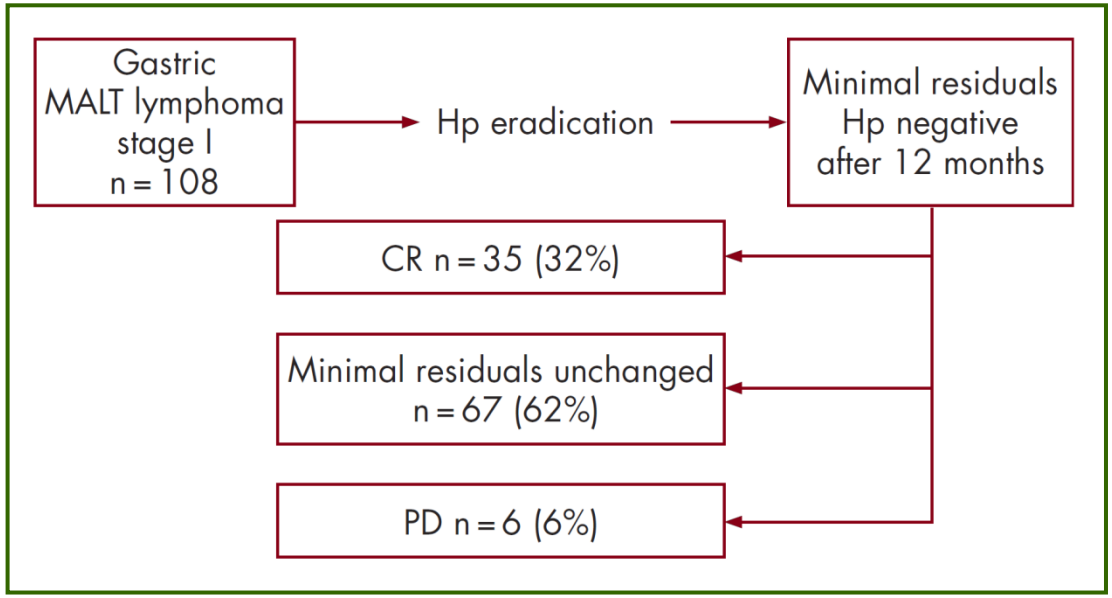
Score	Description	Histologic Features
CR	*Complete histologic remission*	Normal or empty LP and/or fibrosis with absent or scattered plasma cells and lymphoid cells in the LP; no LELs
pMRD	*Probable minimal residual disease*	Empty LP and/or fibrosis with aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM; no LELs
rRD	*Responding residual disease*	Focal empty LP and/or fibrosis; dense, diffuse or nodular lymphoid infiltrate, extending around glands in the LP. Focal LELs or absent
NC	*No change*	Dense, diffuse or nodular lymphoid infiltrate with LELs (LELs “may be absent”)

Abbreviations: GELA, Groupe d'Etude des Lymphomes de l'Adulte; MALT, mucosa-associated lymphoid tissue; LP, lamina propria; LEL, lymphoepithelial lesion; MM, muscolaris mucosa; SM, submucosa

Copie-Bergman et al. Br J Haematol. 2013

Treatment of gastric MALT Lymphoma

Long term f-up after H. pylori eradication (EGILS survey)



At a median follow up of 42 months from successful eradication of *H pylori,* most patients with minimal histological residuals of gastric MALT lymphoma had a favourable disease course without oncological treatment and were managed safely by a watch and wait strategy

Fischbach et al. Gut, 2007

Treatment of gastric MALT Lymphoma

Long-term outcome after H. pylori eradication

Study	N	Follow-up	Lymphoma remission after HP eradication	5-yr OS
Wundisch et al. *J Clin Oncol 2005*	120	75 months	80%	90
Stathis et al. *Ann Oncol 2009*	108	76 months	76%	92
Andriani et al. *Dig Liver Dis. 2009*	60	65 months	88%	95
Nakamura et al. *Gut 2012*	420	72 months	77%	99

Not only patients with molecular residual disease may remain stable but also those with minimal histological MALT lymphoma residuals.
A watch and wait policy seems safe in patients with MRD or histological-only local relapse

Follow-up policies after antibiotics

- Histological relapses tend to be self-limiting
- In the case of histological relapse (without distant dissemination or gross endoscopic tumour) a watch and wait policy can be adopted
- Patients with gastric MALT lymphoma have a 6 times higher risk for gastric adenocarcinoma

Treatment of gastric MALT Lymphoma

Treatment of patients who failed antibiotics and non gastric cases

- Both radiotherapy and chemotherapy have a curative potential
- Favorable outcomes irrespective of treatment type

EGILS Consensus Report
ESMO Guidelines Consensus Conference

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Radiotherapy in gastric MALT lymphoma

Author	n	RT dose (Gy)	FFP
Schechter, 1998	17	28-43	100% at 2 yr
Tsang, 2001	9	20-30	100% at 5 yr
Yahalom, 2002	51	30 median	89% at 4 yr
Hitchcock, 2002	9	34 median	78% (100% local)

- **optimal RT volume, dose and technique?**
- **does this really translate to cure?**
- **in a very indolent condition, is the potential toxicity acceptable?**
- **long term safety? (malignancy, gastric and renal toxicity)**

RT Toxicity can be reduced using modern 3D techniques and minimizing the RT dose to the kidneys and the liver

excellent local control in non-gastric sites , too!

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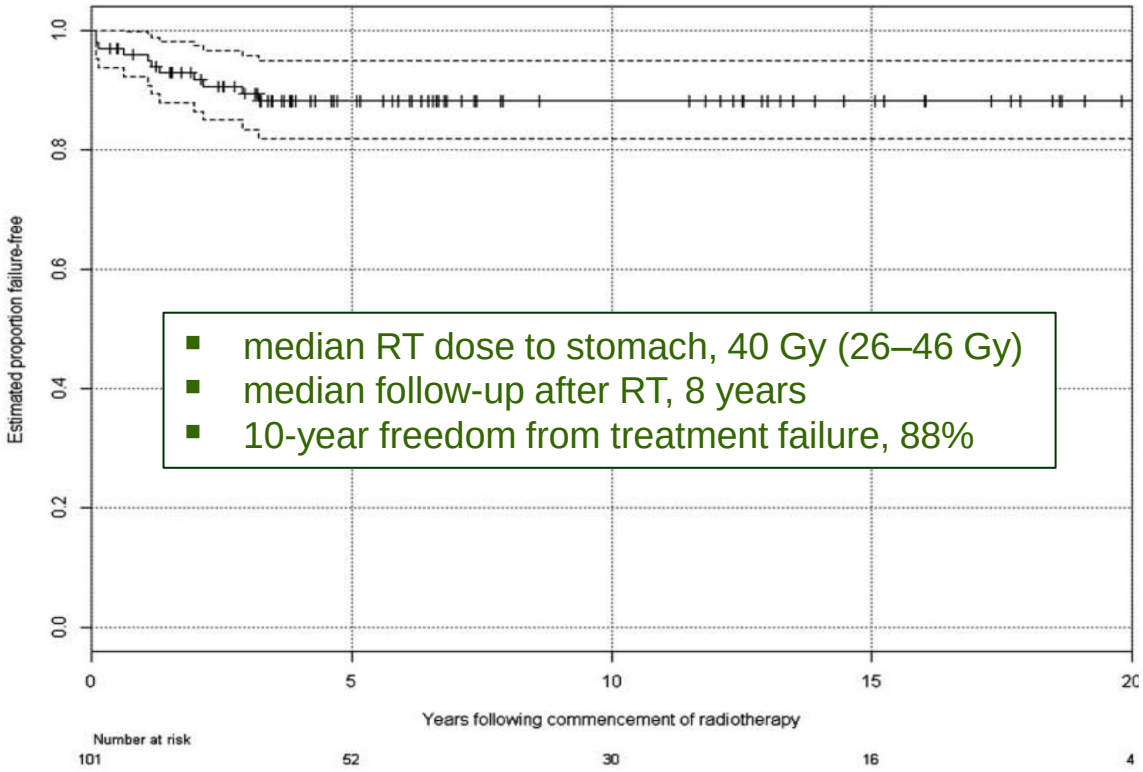
IELSG survey of radiotherapy in gastric MALT lymphoma

102 patients (58 untreated)

RT fields included stomach/involved nodes in 61 patients and whole abdomen in 41.

Risk factors for treatment failure:
- large-cell component
- exophytic growth pattern

RT field size, RT dose not associated with failure



Wirth et al. Ann Oncol 2013

Chemotherapy in gastric MALT lymphoma

- Single alkylating agents: 100% ORR (75%CR) *(Hammel 1995)*
- Cladribine: 100% ORR with higher CR rate in gastric cases (important hematologic toxicity grade and increased MDS risk) *(Jaeger 2002 and 2006)*
- Chlorambucil/Mitoxantrone/Prednisone and Fludarabine/Mitoxantrone as well as the classic CVP are active and well-tolerated regimens *(Wohrer 2003; Zinzani 2004)*
- R-CHOP(-like) only for histologic transformation or bulky masses *(Thieblemont 2005)*
- One randomised trial: better EFS with R-Chlorambucil *(Zucca 2010)*
- R-Bendamustine: 98% CR in a phase 2 study *(Salar 2013)*

Treatment of gastric MALT Lymphoma

Treatment of patients who failed antibiotics and non gastric cases

- Involved-field radiotherapy:
  - 30 to 40 Gy to the stomach and regional nodes in 15-20 fractions using modern radiation techniques
- Chemotherapy and/or immunotherapy:
  - effective in patients with MALT lymphoma of all stages
- Both radiotherapy and chemotherapy can be curative potential and there is no definitive evidence in favor of one of these two modalities
- Surgery restricted to the treatment of complications
- If clinical trials are available, patients should be included

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Thanks for your attention

ANY QUESTIONS ?

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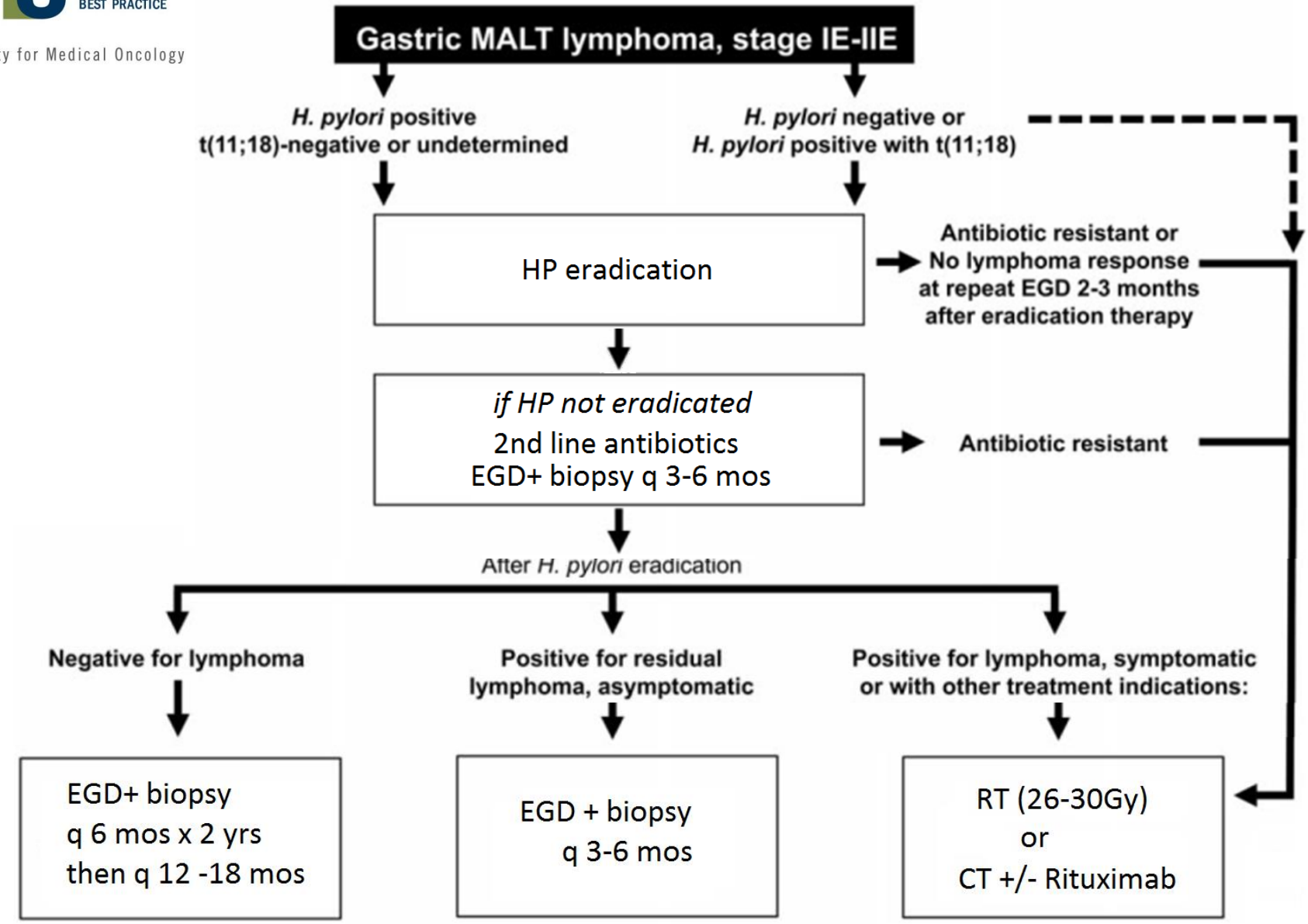
Localized gastric MALT lymphoma: treatment algorithm



E. Zucca et al. Ann Oncol 2014

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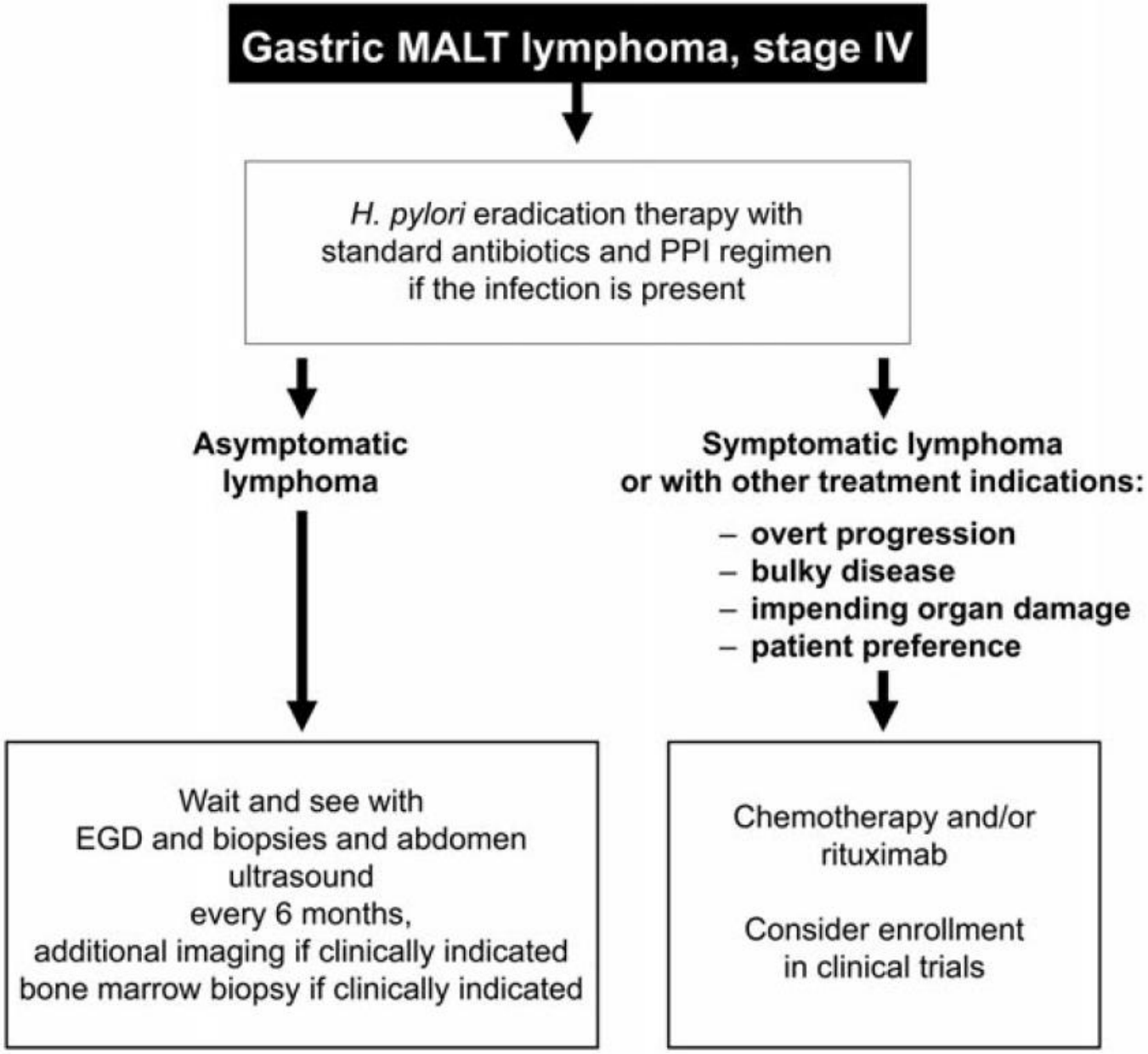
Advanced gastric MALT lymphoma: treatment algorithm



Zucca et al.
Ann Oncol 2014