Indolent Lymphoma

Cancer Centre of Southeastern Ontario
Standard Management Guidelines

Intended for use by Clinicians and Health Care Providers involved in the Management or Referral of adult patients with Indolent lymphoma

Section	Activity	Activity Description	Details	Reference(s)
AA	Cancer Centre Referrals		All patients with a potential or confirmed lymphoproliferative disorder should be referred to the cancer centre.	
A	Diagnosis	Biopsy Type	Excisional biopsy is optimal. Core needle biopsy may be adequate however this should be reviewed on a case by case basis. Pathology review by a lymphoma pathologist recommended.	
B	History and Physical Exam		Standard history and physical exam including disease related symptoms, ECOG performance status, palpable lymphadenopathy, organomegaly or masses.	
C	Investigations		Baseline investigations to be obtained prior to therapy: 1. CBC and differential, electrolytes, creatinine, calcium, albumin, total bilirubin, AST/ALT, ALP, LDH 2. Consider total protein, serum and urine protein electrophoresis and quantitative immunoglobulins 3. In the setting of an IgM monoclonal protein also consider baseline DAT, cryoglobulins, serum viscosity 4. Hepatitis B serology (Hepatitis B surface antibody, surface antigen and core antibody) 5. If Hepatitis B surface antigen is positive or hepatitis B surface antigen is negative but hepatitis B core antibody or surface antibody is positive in the absence of vaccination the patient should have HBV DNA PCR performed and prophylaxis/treatment considered in consultation with	

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			hepatology 6. Consider Hepatitis C and HIV serology 7. Pregnancy test in women of child bearing age 8. CT scan chest, abdomen and pelvis with or without neck 9. Consider baseline PET CT for limited stage follicular lymphoma when curative therapy is being considered 10. Bone marrow aspirate and biopsy with flow cytometry if upstaging would result in a change in management, not required for patients who have undergone baseline PET scan 11. In the setting of relapsed disease, complete restaging and re-biopsy should be considered to evaluate for transformation 12. MUGA or echocardiogram for any patient who will receive anthracyclines 13. Consideration of fertility preservation and sperm banking 14. Tumor lysis prophylaxis should be considered for high risk patients. Allopurinol will suit in most settings however should not be administered concomitantly with Bendamustine, as the risk of serious rash is increased. As an alternative, a single dose of Rasburicase 6mg IV can be administered on Day 1 of Cycle 1 of Bendamustine in the chemotherapy room. Consider screening for G6PD deficiency prior to Rasburicase, and to check a uric acid level on ice on Day 2 of the cycle. If uric acid is still elevated, a second dose of Rasburicase 6mg IV can be administered	
D	Pathology of diagnostic	Synoptic report	Immunohistochemistry, flow cytometry and fluorescence in situ hybridization (FISH) should be performed as per the World	

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	specimen		Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues as well as an ancillary testing as indicated (ie. Molecular clonality, EBER, etc.)	
E	Staging		Groups: I. Involvement of a single lymphatic site (i.e. nodal region, Waldeyer's ring, thymus or spleen) (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE) (rare in Hodgkin lymphoma). II. Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of regions involved may be indicated by a subscript, as in, for example, II_3 III. Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE,S). Splenic involvement is designated by the letter S. IV. Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but	

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			in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow, lungs (other than by direct extension from another site), or cerebrospinal fluid. Modifiers for Group: E Extranodal S Spleen A & B classification A Asymptomatic B Symptoms: fevers, night sweats, weight loss To guide therapy, patients can be separated into two categories by group: 1. Limited Stage: Group IAE or IIAE, nonbulky and involvement of 3 or less adjacent lymph node regions 2. Advanced stage: Stage II involving greater than 3 or nonadjacent lymph node regions, stage III or IV, B symptoms or bulky disease (definition of bulky disease remains controversial however consider 7.5cm or greater)	
F	Follow-up and Restaging		Prior to each chemotherapy: 1. Brief history and physical examination to evaluate disease status, toxicity and performance status 2. CBC, differential +/- electrolytes, creatinine, ALT/AST, total	

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			bilirubin Disease Follow up by CT scanning: 1. After 2-4 cycles of chemotherapy to evaluate interim response 2. At the end of treatment if interim scan was abnormal 3. No additional follow up scans are required, as per the discretion of the treating physician	
G	Follow up with no evidence of disease		After treatment for lymphoma, patients should be followed every 3 to 6 months for the first two years then every 6 to 12 months for three years then annually thereafter. After the initial five years of follow up patients may be discharged to their family physician for ongoing surveillance. In addition to monitoring for relapse, follow up includes surveillance for complications of disease and therapy. 1. Patients should be screened annually for hypothyroidism if the thyroid was irradiated as part of treatment. 2. Second malignancy. Patients should undergo all age appropriate screening for malignancy, and women who have had chest or axillary radiation should start breast cancer screening early, at age 40 or ten years after radiation therapy, whichever comes first. Breast MRI should be performed in addition to mammography. 3. Cardiovascular disease. Patients having undergone chest radiation should have annual screening for hypertension, diabetes and hyperlipidemia and should have aggressive cardiovascular risk reduction.	

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H	Low grade lymphoma including follicular, marginal zone lymphoma (EXCEPT MALT) and lymphoplas-macytoid lymphoma	Limited stage disease, IA or IIA non bulky contiguous	IFRT should be considered in any patient with an apparently localized indolent B cell lymphoma as there is a chance of long term remission This is considered the standard of care for follicular lymphoma as per the Canadian Evidence Based Guidelines for the First Line Treatment of Follicular Lymphoma Alternatively, chemoimmunotherapy as per advanced stage +/- IFRT can be considered Observation alone is a reasonable alternative should the risks of IFRT outweigh the potential benefit	[6]
		Advanced stage disease	Watchful waiting is appropriate for asymptomatic patients with clinical review every 3-6 months Indications for systemic therapy can include: patient symptoms, bulky lymphadenopathy or hepatosplenomegaly, organ compromise, cytopenias due to marrow infiltration, patient preference **First line therapy for advanced low grade lymphoma:** Bendamustine and rituximab (BR) x 6 cycles followed by maintenance Rituximab every 3 months for 2 years *Note: Patients with grade 3b follicular lymphoma or mixed	

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			follicular and diffuse large B cell lymphoma should receive R-CHOP instead as per the DLBCL protocol but should also receive maintenance Rituximab Consolidation with high dose chemotherapy followed by autologous stem cell rescue or radioimmunotherapy is not recommended in the first line setting	
		Relapsed disease	The same principles guiding indications for treatment in the first line setting also apply to the relapsed setting. There is no urgent need to re-initiate therapy in the asymptomatic patient When therapy is indicated no one strategy can be recommended in the relapsed setting, rather therapy should be individualized based on patient and disease factors such as patient age, performance status and comorbidities as well as prior therapy, stage, disease location and responsiveness **Treatment options include:** R-Bendamustine (retreatment if prolonged disease free interval) Ibrutinib R-CHOP R-CVP Chlorambucil +/- rituximab Oral or IV cyclophosphamide +/- rituximab Fludarabine based regimens GDP	

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			ICE Mini-BEAM DHAP Idelalisib Obinatuzumab Additionally in the case of **lymphoplasmacytoid lymphoma**, bortezomib and lenolidamide have shown efficacy in the setting of relapsed disease *Note: not all of these options are presently publicly funded, please see the Cancer Care Ontario website for a full list of funded regimens https://www.cancercare.on.ca/toolbox/drugformulary/stfmregimens/ High dose chemotherapy followed by autologous stem cell rescue is recommended in eligible patients after response is shown to systemic therapy in the setting of a first or second relapse. Allogeneic stem cell transplantation can also be considered in eligible patients in the setting of a 2nd or 3rd chemosensitive relapse. Patients should also always be considered for enrollment in clinical trials, available locally or through the clinicaltrials.gov website.	

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			Symptomatic and palliative therapy including palliative radiation should be considered in patients with refractory disease or those with poor performance status	
I	Mantle cell lymphoma		As opposed to other indolent B cell lymphomas, mantle cell lymphoma is associated with a short median survival, typically of 3-5 years. Fitter patients who are treated with more intensive cytarabine containing induction therapy followed by consolidation with autologous stem cell transplant seem to experience an improvement in progression free survival. There are issues of increased toxicity however, and conventional chemoimmunotherapy followed by consolidation with high dose chemotherapy and autologous stem cell rescue may also result in a good long term outcome Although most patients will have steadily progressive disease at presentation requiring therapy, a small subset who are asymptomatic with a low burden of disease may be initially managed with watchful waiting similar to the other indolent B cell lymphomas	[7], [9], [10], [11]
		Limited stage	In the rare patient who presents with stage IA or IIA contiguous disease there is a chance of long term remission with IFRT +/- bendamustine plus rituximab x 6 cycles	
		Advanced stage	**In patients under the age of 60 recommend:** Sequential R-CHOP/R-DHAP x 6 cycles followed by autologous stem cell transplant (GELA) OR	

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			R-Bendamustine x 6 cycles followed by autologous stem cell transplant Consider maintenance Rituximab after transplant every 3 months for 2 years **In patients over the age of 60, recommend:** R-Bendamustine x 6 cycles* followed by autologous stem cell transplant if eligible and maintenance Rituximab every 3 months for 2 years in either case *Note is made of recent evidence in favor of adding cytarabine 500mg/m2 to each cycle of R-Bendamustine (R-BAC-500) in elderly patients not eligible for transplant. This regimen is funded.	
		Relapsed disease	There is no urgent need to re-initiate therapy in the asymptomatic patient When therapy is indicated no one strategy can be recommended in the relapsed setting, rather therapy should be individualized based on patient and disease factors such as patient age, performance status and comorbidities as well as prior therapy, stage, disease location and responsiveness **Treatment options include:** R-Bendamustine Ibrutinib	

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			R-CHOP R-CVP Chlorambucil +/- rituximab Oral or IV cyclophosphamide +/- rituximab Fludarabine based regimens Idelalisib Bortezomib Lenolidomide HyperCVAD DHAP Mini-BEAM GDP ICE *Note: not all of these regimens are publicly funded, please see the Cancer Care Ontario website for a full list of funded regimens https://www.cancercare.on.ca/toolbox/drugformulary/stfmregimens/ Allogeneic stem cell transplantation can also be considered in eligible patients in the setting of a 2nd or 3rd chemosensitive relapse. Symptomatic and palliative therapy including palliative radiation should be considered in patients with refractory disease or those with poor performance status	

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J	Gastric extranodal marginal zone lymphoma		In addition to the recommended investigations in section C, initial staging must include upper endoscopy with multiple biopsies taken from each region of the stomach, duodenum and gastroesophageal junction, and any site with abnormal appearance. Histology should include stains for Helicobacter pylori. If histology is negative for H. Pylori, recommend a second form of testing such as the urea breath test. FISH for t(11;18) should be considered. Lugano staging: Stage I-The tumor is confined to the gastrointestinal tract. It can be a single primary lesion or multiple, noncontiguous lesions Stage II-The tumor extends into the abdomen. This is further subdivided based upon the location of nodal involvement: • Stage II_1: Involvement of local nodes (paragastric nodes for gastric lymphoma) • Stage II_2: Involvement of distant nodes (para-aortic, para-caval, pelvic or inguinal nodes) • Stage II_E: The tumor penetrates the serosa to involve adjacent organs or tissues Stage III-There is no stage III disease in this system Stage IV-There is disseminated extranodal involvement or concomitant supra-diaphragmatic nodal involvement	[12], [13]
		Limited stage (I/II)	Stage I or II disease, H. pylori positive, t(11;18) negative: -H. pylori eradiation therapy and repeat urea breath test 2-3 months after to check for eradication, second line antibiotic	

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			regimen recommended at that point if H. Pylori still detected, wait another 2 months prior to repeating urea breath test -When H. pylori found to be negative, repeat staging with endoscopy +/- CT (if lymph node involvement) for early response assessment Stage I or II disease, H. pylori positive, t(11;18) positive: -IFRT with curative intent* and H. Pylori eradication therapy as above -Single agent Rituximab can be used as an alternative to IFRT if there is a contraindication to radiation Stage I or II disease, H. pylori negative: -IFRT with curative intent* and H. Pylori eradication therapy as above -Single agent Rituximab can be used as an alternative to IFRT if there is a contraindication to radiation *Note: consideration can be given to H. pylori eradication as the sole initial therapy in these cases. IFRT should then be used if there are no signs of lymphoma regression at EGD follow up 2 to 3 months after eradication therapy. Repeat staging with endoscopy +/- CT (for ongoing lymphadenopathy) every 6 months until CR then endoscopy alone every 6 months for the first 2 years then yearly for 3 years then as	

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			dictated by patient symptoms. Consider ongoing annual endoscopy on a case by case basis for those patients deemed at particularly high risk of gastric cancer, to be determined in conjunction with gastroenterology It may take 12-18 months for the lymphoma to recede. Features with higher risk of eradication failure include regional lymphadenopathy, deep gastric wall invasion, or other chromosomal translocations which involve MALT1 or Bcl-10. If there is minimal response in this patient population, consider moving on to second line therapy with radiation before reaching the 18 month guideline -If the lymphoma persists or recurs 12-18 months after successful H. pylori eradication, recommend IFRT with curative intent, or -Single agent Rituximab can be used as an alternative to IFRT if there is a contraindication to radiation, or if there is persistent or recurrent disease after radiation	
		Advanced stage (IIE, IV)	H. pylori eradication therapy should be given to all patients with gastric MALT regardless of stage or H. pylori test status (negative/positive) Otherwise manage as per advanced stage low grade lymphoma	
K	Clinical Trials		Link to Cancer Centre of Southeastern Ontario Clinical Trials	

References

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3. Alberta Health Services Lymphoma Clinical Practice Guidelines, LYHE-002, Version 8, February 2016.

4. BC Cancer Agency Malignant Lymphoma Cancer Management guidelines, last accessed November 2016.

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9. Delarue R, Haioun C, Ribrag V, et al. CHOP and DHAP plus rituximab followed by autologous stem cell transplantation in mantle cell lymphoma: a phase 2 study from the Groupe d'Etude des Lymphomes de l'Adulte. Blood 2013: 121; 48-53. [back]

10. Tefferi A and Vose J. CME information: Mantle Cell Lymphoma: 2015 Update on Diagnosis, Risk-Stratification and Clinical Management. AJH 2015: 90; 739-745. [back]

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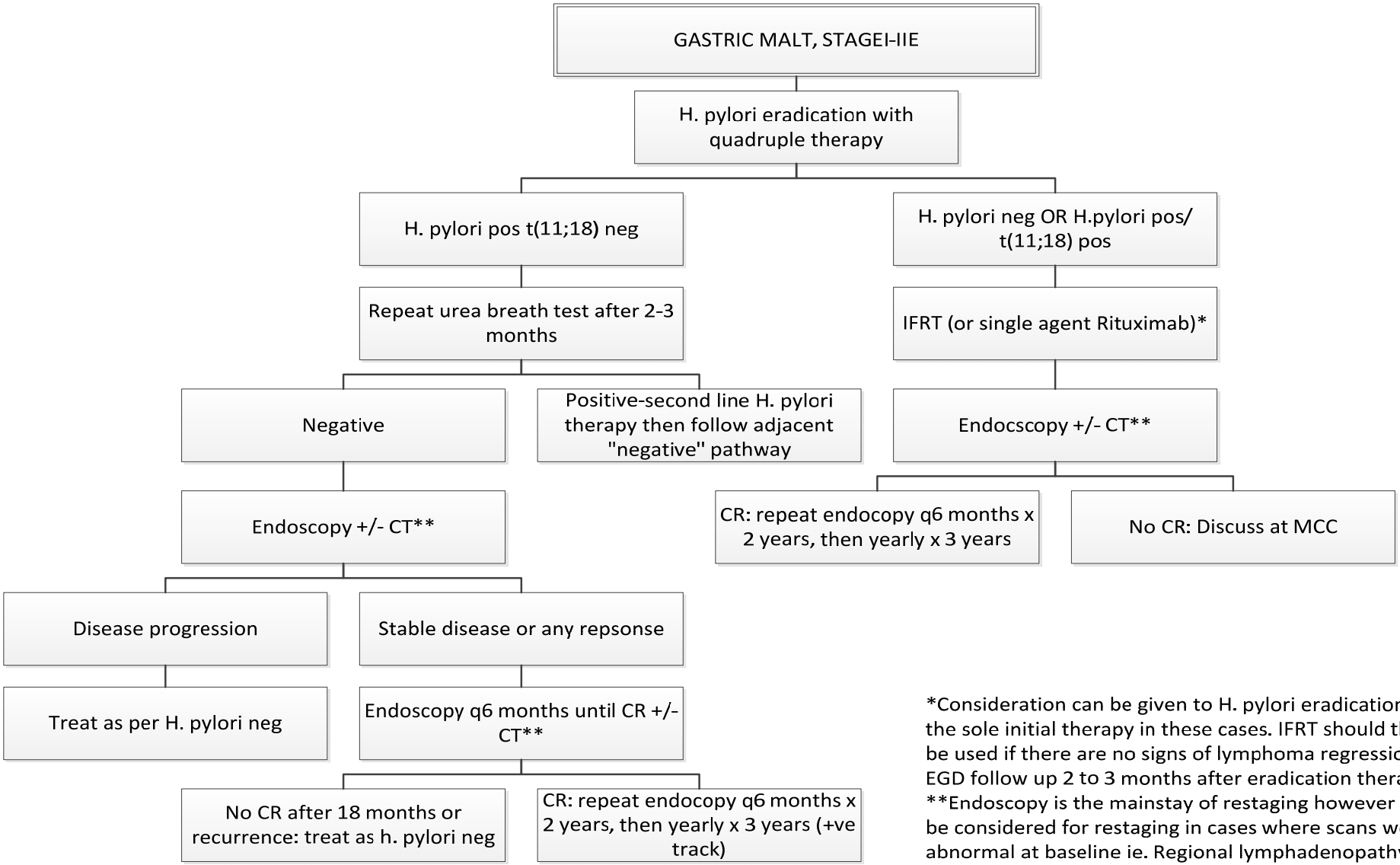
12. Zucca E, Copie-Bergman C, Ricardi U, Thieblemont C, Raderer M, Ladetto M on behalf of the ESMO Guidelines working group. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Annals of Oncology 2013; 24: vi144-vi148. [back]

13. Zucca E, Bertoni F. The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. Blood 2016; 127: 2082-2092. [back]

Revisions

1. Added section L – link to Cancer Centre Clinical Trials - Janice

Appendix 1 - Malt Lymphoma Algorithm



*Consideration can be given to H. pylori eradication as the sole initial therapy in these cases. IFRT should then be used if there are no signs of lymphoma regression at EGD follow up 2 to 3 months after eradication therapy.
**Endoscopy is the mainstay of restaging however CT to be considered for restaging in cases where scans were abnormal at baseline ie. Regional lymphadenopathy